EXHIBIT “A”

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

UNITED THERAPEUTICS CORPORATION,	)	
	)	Civil Action No. 12-1617 (PGS)(LHG)
Plaintiff,	)	
v.	)	
SANDOZ, INC.,	)	
Defendant.	)	

DEFENDANT SANDOZ INC.'S INVALIDITY CONTENTIONS

Pursuant to Local Patent Rule 3.3 and the Court's August 7, 2012 Scheduling Order, Defendant-Counterclaim Plaintiff Sandoz Inc. ("Sandoz") hereby submits its Invalidity Contentions. Sandoz asserts that claims 1-2 of U.S. Patent No. 5,153,222 ("the '222 patent"), claims 1-4 of U.S. Patent No. 6,765,117 ("the '117 patent"), and claims 1-5, 7-17, and 19-26 of U.S. Patent No. 7,999,007 ("the '007 patent") are invalid under the patent statutes.

I. LEGAL STANDARDS FOR INVALIDITY

A. Legal Standards for Anticipation

Anticipation is a question of fact that is shown and reviewed under a clearly erroneous standard. *E.g., Rapoport v. Dement*, 254 F.3d 1053, 1057-58 (Fed. Cir. 2001). A patent claim is invalid for anticipation where each and every element of the claimed invention is disclosed in a single prior art reference. 35 U.S.C. § 102; *In re Paulsen*, 30 F.3d 1475, 1478-79 (Fed. Cir. 1994). "[W]hen a patent claims a chemical composition in terms of ranges of elements, any single prior art reference that falls within each of the ranges anticipates the claim." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1346 (Fed. Cir. 1999).

To find anticipation, the four corners of a single prior art document must describe each and every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation. *Advanced Display Sys. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000). Thus, a prior art reference without express reference to a claim limitation may nonetheless anticipate by inherency. *Perricone v. Medicis Pharmaceutical Corp.*, 432 F.3d 1368, 1375-76 (Fed. Cir. 2005). "Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claim limitations, it anticipates." *Id.*; *Continental Can Co. U.S.A., Inc. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991) (Under the theory of inherent anticipation, if an element is not expressly disclosed in the prior art reference, the reference still will be deemed to anticipate the subsequent claim if the missing element "is necessarily present in the thing described in the reference").

"[I]nherency is not necessarily coterminous with the knowledge of those skilled in the art. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art." *Perricone*, 432 F.3d at 1376; *see also Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1378 (Fed. Cir. 2003) (concluding that inherent anticipation does not require that a skilled artisan recognize the inherent characteristic in the prior art that anticipates the claimed invention). A previously unrecognized benefit of an known process or method may be viewed as a "newly discovered result[] of [a] known process[] directed to the same purpose," and is thus anticipated. *Bristol-Myers Squibb Co. v. Ben Venue Labs. Inc.*, 246 F.3d 1368, 1376-77 (Fed. Cir. 2001) citing *In the case of Application of May*, 574 F.2d 1082 (C.C.P.A. 1978); *Perricone*, 432 F.3d at 1377-78; *King Pharmaceuticals, Inc. v. Elan Pharmaceuticals, Inc.*, 616 F.3d 1267, 1275-76 (Fed. Cir. 2010). "A court may resolve factual questions about the references in the

prior art by examining the reference through the eyes of a person of ordinary skill in the art, among other sources of evidence about the meaning of the prior art." *Schering*, 339 F.3d at 1377-78. In other words, although past recognition of the inherent feature is not necessary, the court may still evaluate the opinions of those skilled in the art to determine the scope of the prior art reference. *Id*. at 1378.

B. Legal Standards for Obviousness.

A patent is invalid for obviousness if "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). The following inquiries are pertinent to resolving this issue: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; and (3) the difference between the prior art and the claims at issue. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Against this background, the obviousness or nonobviousness of the subject matter is determined. *Id*. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, *etc.*, might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. *Id*. Obviousness is not determined in hindsight in view of the invention in question. Instead, prior art is considered by the hypothetical artisan at a time just before the invention was made. *Al-Site Corp. v. VSI Int'l*, 174 F.3d 1308, 132 (Fed. Cir. 1999).

A reference must be considered for all that is taught – disclosures that diverge and teach away from the invention as well as disclosures that point toward and teach the invention. *See In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). A reference teaches away if it would have led a person skilled in the art in a direction different from that taken by the inventor. *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 885 (Fed. Cir. 1998).

"The degree of teaching away will of course depend on the particular facts; in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by" the inventor. *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). It is impermissible to select only those portions of a reference that support a given position and exclude other parts necessary to the full appreciation of what the reference fairly teaches. *Bausch & Lomb, Inc. v. Barnes-Hind*, 796 F.2d 443, 448 (Fed. Cir. 1986).

The United States Supreme Court has clarified certain aspects of the obviousness analysis, particularly with respect to the Federal Circuit's requirement that there be a "teaching suggestion, or motivation" to combine the teachings of two or more separate references. In *KSR Int'l Co. v. Teleflex, Inc.*, 127 S.Ct. 1727 (2007), the Court expressly rejected a rigid requirement for a motivation to combine, stating:

> [t]he obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents. The diversity of inventive pursuits and of modern technology counsels against limiting the analysis in this way.

KSR, 127 S.Ct. at 1741. The Court further stated:

> [i]n determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls. What matters is the objective reach of the claim. If the claim extends to what is obvious, it is invalid under §103. One of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims.

KSR, 127 S.Ct. at 1741-1742. Instructing that the obviousness analysis should not be limited by looking only at the problem that the patentee was trying to solve, the Court stated:

> [t]he question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person with ordinary skill in the art. Under the correct analysis, any need or problem known in the

> field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.

KSR, 127 S.Ct. at 1742. The Court noted that in some instances, the fact that it may have been "obvious to try" to make a claimed invention may be dispositive:

> [w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103.

Id.

When examining the obviousness of a compound and/or a method of using that compound, structural similarity alone may be sufficient to give to an expectation that two compounds with similar structures will have similar properties. *In re Merck*, 800 F.2d 1091 (Fed. Cir. 1986), *citing In re Payne*, 606 F.2d 303, 313 (C.C.P.A. 1979). Structural similarity between a claimed compound and prior art compounds creates a *prima facie* case of obviousness. *In re Dillon*, 919 F.2d 688 (Fed. Cir. 1990). The burden then falls on an applicant to rebut that *prima facie* case. *Id*. at 693. A rebuttal or counter-argument can consist of test data showing that the claimed compounds possess unexpectedly improved properties from the prior art compounds. All evidence of the properties of the claimed and prior art compounds must be considered in determining the ultimate question of patentability.

The "discovery," however, that the claimed compound possesses a property not disclosed in the prior art does not by itself defeat a *prima facie* case of obviousness. *In re Dillon*, 919 F.2d at 693. *See also In re Merck*, 800 F.2d at 1099, where the Federal Circuit stated:

> [t]he core of it is that, while there are some differences in degree between the properties of amitriptyline and imipramine, the compounds expectedly have the same type of biological activity. In the absence of evidence to show that the properties of the compounds differed in such an appreciable

> degree that the difference was really unexpected, we do not think that the Board erred in its determination that appellant's evidence was insufficient to rebut the *prima facie* case.

Evidence of secondary considerations, if present, must be considered in determining obviousness, but there must be a nexus between such evidence and the merits of the claimed invention. *Graham*, 383 U.S. at 17. The existence of such evidence, however, does not control the obviousness determination. *Richardson-Vicks v. Upjohn Co.*, 122 F.3d 1476, 1483 (Fed. Cir. 1997). Examples of secondary considerations are commercial success, copying, prior failure of others, licenses under the patent, a long-standing need for the invention, unexpected results, skepticism by others in the art, and contemporaneous development by others. *Graham*, 383 US. at 17-18; *DMI, Inc.*, 802 F.2d at 425. Commercial success is not a relevant factor in determining obviousness where others were legally barred from practicing the invention. *Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1376-77 (Fed. Cir. 2005).

II. CLAIMS 1 AND 2 OF THE '222 PATENT ARE INVALID UNDER 35 U.S.C. §§ 102 AND 103

A. Introduction.

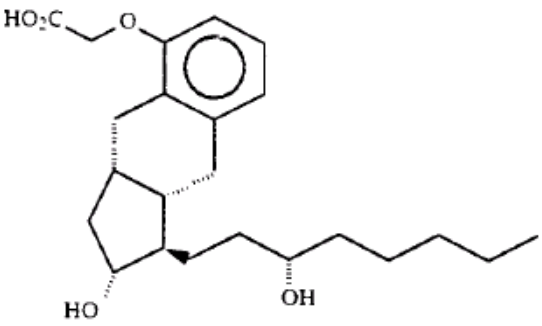
U.S. patent application serial No. 715,439, which ultimately issued as the '222 patent, was filed on June 14, 1991 as a divisional application of U.S. Application Ser. No. 367,090, filed June 16, 1989 and subsequently abandoned. The '222 patent claims priority to Great Britain Patent No. 881438, filed on June 17, 1988. (Thus, June 17, 1988 is the critical date for purposes of prior art). The '222 patent issued on October 6, 1992 and lists Anjaneyulu S. Tadepalli, Walker A. Long, James W. Crow, and Kenneth B. Klein as inventors. The patent is assigned to Burroughs Wellcome Co. on its face.[1]

[1] Plaintiff, United Therapeutics Corporation ("UTC") alleges that the '222 patent was subsequently assigned to UTC.

Claims 1 and 2 of the '222 patent are method claims directed to the treatment of pulmonary hypertension in a patient by administering an effective amount of the compound 9-deoxy-2',9α-methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-13,14-dihydro-prostaglandin F_1 ("treprostinil"), or a pharmaceutically acceptable salt thereof. Specifically, the claims read as follows:

> 1. A method of treating pulmonary hypertension in a patient, which comprises administering to said patient an effective pulmonary hypertension treatment amount of the compound 9-deoxy-2',9α-methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)- 13,14-dihydro-prostaglandin F_1.
>
> 2. A method of treating pulmonary hypertension in a patient, which comprises administering to said patient an effective pulmonary hypertension treatment amount of a pharmaceutically acceptable salt of the compound 9-deoxy-2',9α-methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)- 13,14-dihydroprostaglandin F_1.

The chemical structure of treprostinil is depicted below. ('222 patent, Col. 3:5-15).



Treprostinil

Treprostinil was developed by employees of the UpJohn Company as a benzindene analogue to prostacyclin (also known as PGX and later PGI_2) in the late 1970s or early 1980s. Treprostinil is described and claimed in U.S. Patent No. 4,306,075 to Aristoff (the "'075 patent"). Although the '222 patent acknowledges that the '075 patent describes novel

benzindene prostaglandins,[2] and briefly describes their physiological functions (including inhibition of blood platelet aggregation, reduction of gastric section and bronchodilation), the '222 patent omits the fact that the '075 patent actually discloses and claims treprostinil itself. (Compare '222 patent, Col. 1:60-68; and '075 patent, Col. 62:5-39; Claim 5).

Prostacyclin (also known as epoprostenol and commercially available under the trade name Flolan) is a naturally occurring compound known for its acute effects in inhibiting platelet aggregation and thrombosis and its potent vasodilatory effects. As discussed below, because of these properties, prostacyclin was well known to be useful in treating diseases involving platelet aggregation, thrombosis and vasoconstriction, such as systemic hypertension, pulmonary hypertension and arthrosclerosis. As the '075 patent teaches, treprostinil (as well as other prostacyclin benzindene analogues) was known to have these same functional properties, and thus, inherently, these same clinical effects.

Since the 1970s, prostacyclin was known to be a potent agent for the treatment of systemic and pulmonary hypertension, based on its anti-platelet aggregation, anti-thromotic and vasodilation properties, *see infra*. Prostacyclin, however, has a very short half life (*i.e.*, less than six minutes) and was found to be unstable at room temperature. Because of these disadvantages, significant efforts were made to develop prostacyclin analogues having similar pharmacological properties but a longer effective life and greater stability.

Treprostinil, a prostacyclin analogue, had been disclosed in various prior art patents and articles, starting with an initial disclosure in the '075 patent in December 1981. The Upjohn Company scientists who first made treprostinil did so with the goal of synthesizing a compound

[2] Prostaglandins are a class of naturally occurring and synthetic compounds, which produce various pharmacological responses. Prostacyclin and its many analogues are members of the prostaglandin class of compounds.

that retained the pharmacological functionality of prostacyclin, but had a longer duration of action and was more stable. Treprostinil satisfied these goals in that it was found to exhibit similar pharmacological functionality and had a longer half life than prostacyclin and greater stability. *Id*. Because of treprostinil's anti-platelet and vasodilation properties, one skilled in the art would have understood treprostinil to be an agent effective in treating pulmonary hypertension well before the invention date of the '222 patent. Thus, the '222 patent claims are anticipated. Moreover, early disclosure of treprostinil and its pharmacological properties, when combined with a significant amount of art disclosing use of prostacyclin for treating pulmonary hypertension based on these very same properties, renders the claimed invention obvious as well.

B. Background on the Use of Prostacyclin and Prostacyclin Analogues to Treat Pulmonary Hypertension.

At the time prostacyclin was discovered, pulmonary hypertension was usually classified as primary or secondary and is defined generally as a sustained elevation of blood pressure in the arteries in the lung. Generally, Wagenvoort, *Pathology of Pulmonary Hypertension* (Wiley & Sons 1977); Braunwald, Heart Disease – A textbook of Cardiovascular Medicine, pp. 835-921 (W.B. Saunders 1980); Jones et al, "Treatment of Primary Pulmonary Hypertension with Intravenous Epoprostenol (Prostacyclin) *Br. Heart J.*, Vol. 57, pp. 270-78 (1987); Long et al, "Prostacyclin and PGE_1 Treatment of Pulmonary Hypertension," *Am. Rev. Respir. Dis.*, Vol. 136, pp. 773-76 (1987); *The Merck Manual*, pp. 650 (1987); *see also* Braunwald Heart Disease, Chapter 78 (2011). Typically, the causes of pulmonary hypertension include vasoconstriction, platelet aggregation and thrombosis. *Id*.

Pulmonary hypertension is considered "primary" if there is no identified cause or condition. Wagenvoort, *Pathology of Pulmonary Hypertension* (Wiley & Sons 1977) at p. 120 ("Wagenvoort"). Early symptoms of primary pulmonary hypertension often include shortness of

breath and fatigue, and patients often live for only a few years after diagnosis. Wagenvoort at p. 120. There is no cure for primary pulmonary hypertension, only treatment to lessen the symptoms and hopefully prolong survival. *See generally* Wagenvoort. Primary pulmonary hypertension is relatively rare and predominantly affects women of child-bearing age, although children, adult males, and the elderly can also be afflicted. Wagenvoort at pp. 120-21.

During the late 1960s, a primary pulmonary hypertension epidemic drew worldwide attention to the disease. In 1968, researchers in Berne, Switzerland noticed a dramatic increase in cases of primary pulmonary hypertension. Wagenwoort at p. 111. Prior to 1967, pulmonary hypertension was considered an extremely rare disease that was diagnosed in 0.87% of patients in whom cardiac catheterization was performed,[3] and by 1968, the incidence increased to 15.4% of such patients. *Id*. Many of these new primary pulmonary hypertension patients had taken aminorex fumarate (Menocil), an appetite-suppressor. *Id*. There was a similar outbreak of primary pulmonary hypertension among people taking aminorex around the same time in Austria and Germany. *Id*. at p. 12. Patients who developed pulmonary hypertension after taking aminorex often developed intimal fibrosis, necrotizing arteritis, and plexiform lesions in their pulmonary arteries, and the disease was usually fatal. *Id*. By the end of 1970, aminorex was removed from the market in all three countries, and by 1972, the incidence of primary pulmonary hypertension had decreased to pre-1967 levels. *Id*.

Pulmonary circulation refers to the flow of blood between the lungs and the heart. The right ventricle pumps de-oxygenated blood into the lungs via the pulmonary arteries. *See generally*, Wagenvoort. Once in the lungs, blood flows through the arteries and capillaries and

[3] Cardiac catheterization is a procedure used to measure pulmonary blood pressure and is used in diagnosing pulmonary hypertension. Wagenvoort at p. 2.

exchanges carbon dioxide for oxygen. *Id*. Oxygen-rich blood then flows through the pulmonary veins to the left side of the heart, where it is pumped to the rest of the body via the systemic circulation. *Id*. Pulmonary blood flow is the amount of blood that passes through the pulmonary arteries and capillaries and into the pulmonary veins in a given amount of time. Braunwald, *Heart Disease - A textbook of Cardiovascular Medicine*, Chapters 24 & 44, at p. 825 (W.B. Saunders 1980)("Braunwald"). Pulmonary blood pressure depends on pulmonary blood flow and vascular resistance to blood flow. Wagenvoort at p. 2; Braunwald at p. 835.

Pulmonary hypertension can be caused by either an increase in resistance to blood flow in the pulmonary arteries or a blockage of the pulmonary veins. Wagenvoort, at p. 9. Pulmonary arteries, unlike systemic arteries, are recruitable. As a result, pulmonary arteries can constrict, causing increased vascular resistance. Wagenwoort 1977, at pp. 2-3; Braunwald, at p. 835. Vasoconstriction can cause permanent functional and morphological alterations in the blood vessels, for example through the formation of various pulmonary lesions. *Id*. These changes in the pulmonary arteries will further inhibit blood flow, thereby further increasing the pulmonary pressure. *Id*. Accordingly, pulmonary hypertension is a progressive disease characterized by a continuous cycle of pulmonary lesion development and rising pulmonary pressure. *Id*. Further, as a result of increased vascular resistance to blood flow, the right ventricle must use more force to effectively pump blood through the lungs, which can lead to right heart failure. *Id*. at p. 10.

As explained above, increasing pulmonary blood pressure results in functional alterations in the pulmonary blood vessels. Wagenwoort at pp. 10, 62-94, 119-142; see generally Braunwald. First, the epithelial cells, which make up the lining the inner walls of the arteries, multiply, causing the arterial wall to thicken. *Id*. Collagen fibers begin to build up along the inner arterial wall, which results in increased vascular resistance. *Id*. This fiber build-up is

characterized as intimal fibrosis. *Id*. In advanced stages of pulmonary hypertension, the blood vessels become completely obstructed. *Id*. Other pulmonary lesions characteristic of advanced stages of pulmonary hypertension include fibrinoid necrosis, arteritis and plexiform lesions.

Fibrinoid necrosis develops when vasoconstriction and increased blood pressure causes epithelial cell death in sections of the arterial wall, which in turn results in the formation of clots caused by aggregation of fibrin and platelets. *Id*. This may cause an inflammatory response, leading to arteritis. *Id*. Over time, epithelial cells located on the interior blood vessel wall carve paths through the aggregation of fibrin and platelets to form thin, tangled channels that allow blood to flow through. *Id*. The resulting tangled mass of channels is called a plexiform lesion. *Id*. Fibrinoid necrosis and plexiform lesions involve functional, morphological changes, and their development indicates that pulmonary hypertension is irreversible. See generally Wagenvoort; Braunwald. In the late 1970s, Wagenvoort noted that while known vasodilators produce a clinical effect in early stages of pulmonary hypertension, once "vascular changes have progressed to a degree in which they have become largely irreversible and in which the vessels have lost their reactivity, the effect as a rule abates or disappears." Wagenvoort at p. 10.

During the 1970s, John R. Vane, Salvador Moncada and other colleagues at the Wellcome Foundation discovered that naturally occurring prostacyclin is a potent inhibitor of platelet aggregation. Moncada & Vane, "The Role of Prostacyclin in Vascular Tissue," New Dev. Prostoglandin and Thromboxane Res., Vol. 38, No. 1, pp. 66-71 (1979); Moncada & Vane, "The Prostacyclin/Thromboxane Balance and Cardiovascular Disease," *Medicine, Science and Society*, pp. 83-113 (Wiley & Sons 1984); Vane, "Prostaglandins and the Cardiovascular System," *Br. Heart. J.*, Vol. 49, No. 5, pp. 405-09 (1983). The team went on to generate a synthetic form of prostacyclin, which they called PGX and later PGI_2, that demonstrated similar

efficacy in inhibiting platelet aggregation. *Id*. They further discovered that synthetic prostacyclin is a much more potent inhibitor of platelet aggregation and vasodilator than other prior known prostaglandins. *Id*.

This work by Vane and his colleagues ultimately lead the Nobel Committee to confer the 1982 Nobel Prize in medicine on Vane. October 11, 1982 Press Release Regarding Nobel Prize in Physiology or Medicine. Vane's and his colleagues' isolation of prostacyclin and discovery of its beneficial vasodilation and anti-thrombotic functionality was described in detail by Vane in his 1982 Nobel lecture article "Adventures and Excursions in Bioassay: The Stepping Stones to Prostacyclin," *Br.J. Pharmac*., Vol. 79, pp. 821-38 (1983), and in other Vane publications. Vane and others quickly seized on the anti-platelet aggregation and vasodilation activity of prostacyclin as a possible treatment for systemic and pulmonary hypertension. *Id*.; Moncada & Vane, "The Role of Prostacyclin in Vascular Tissue," *New Dev. Prostoglandin and Thromboxane Res.*, Vol. 38, No. 1, pp. 66-71 (1979); Moncada & Vane, "The Prostacyclin/Thromboxane Balance and Cardiovascular Disease," *Medicine, Science and Society*, pp. 83-113 (Wiley & Sons 1984); Vane, "Prostaglandins and the Cardiovascular System," *Br. Heart. J.*, Vol. 49, No. 5, pp. 405-09 (1983). Later, tests confirmed that prostacyclin was effective in treating pulmonary hypertension in humans. It was also noted that, unlike some prostaglandins, prostacyclin is not metabolized in the lungs, and, in fact, is a potent vasodilator, in the pulmonary arterial system. Armstrong et al, "Comparison of the Vasodepressor Effects of Prostacyclin and 6-oxo-Prostacyclin F_1 with those of Prostaglandin E_2 in Rats and Rabbits," *Br. J. Pharmac.*, Vol. 62 pp. 125-30 (Jan. 1978); Dusting et al, "Prostacyclin (PGX) is the Endogenus Metabolite Responsible for Relaxation of Coronary Arteries Induced by Arachidonic Acid," *Prostaglandins*, Vol. 13, No. 1, pp. 3-15 (Jan. 1977);

Barst, "Pharmacologically Induced Pulmonary Vasodilation in Children and Young Adults with Primary Pulmonary Hypertension," *Chest*, Vol. 86, pp. 497-503 (April 1986); Hanley, "Prostaglandins and the Lung," *Lung*, Vol. 164, pp. 67-77 (1986); Hyman et al, "Prostaglandins and the Lung," *Am. Review of Resp. Disease*, Vol. 117, pp. 111-36 (1978); Jones, "Treatment of Primary Pulmonary Hypertension with Intravenous Epoprostenol (Prostacyclin)," *Br. Heart J.*, Vol. 57, pp. 270-78 (1978); Long et al, "Prostacyclin and PGE_1 Treatment of Pulmonary Hypertension," *Am. Rev. Respir. Dis.*, Vol. 136, pp. 773-76 (1987).

Prostacyclin, however, suffers from certain known disadvantages as a therapy. First, its half life is short – less than 6 minutes. Long, *Am. Rev. Resp. Dis*. at pp. 775; Jones, *Br. Heart J*. at pp. 276-77; Moncada et al, "Arachidonic Acid Metabolites and the Interactions between Platelets and Blood Vessel Walls," *Physiology in Medicine – New Eng. J. of Med.*, Vol. 300, No. 20, pp. 1142-47 (May 1979); Moncada et al, "The Prostacyclin/Thromboxane Balance and Cardiovascular Disease," *Medicine, Science and Society*, pp. 83-113 (Wiley & Sons 1984); Ubatuba et al "The Effect of Prostacyclin (PGI_2) on Platelet Behavior, Thrombus Formation In Vivo and Bleeding Time," *Thrombos. Haemostas*, pp. 425-35 (Stuttz, 1979). Second, prostacyclin is unstable at room temperature and at a neutral pH. *Id*. Consequently, significant efforts were made in the late 1970s and early 1980s to synthesize prostacyclin analogues that would maintain prostacyclin's anti-platelet aggregation and vasodilation properties, while also having a longer half life and greater stability. Nickolson et al, "Prostacyclin Analogs," *Medicinal Research Rev*., Vol. 5, No. 1, pp. 1-53 (1985); Whittle et al, "Antithrombotic Assessment and Clinical Potential of Prostacyclin Analogues, *Progressin Med. Chem.*, Vol. 21, pp. 238-79 (1984); Whittle et al, Platelet Actions of Stable Carbocyclic Analogues of Prostacyclin," *Circulation*, Vol. 72, pp. 1219-25 (1985).

During this period, scientists at the UpJohn Company developed and tested numerous prostacyclin analogs, and one such analogue was treprostinil. Aristoff et al, "Synthesis and Structure – Activity Relationship of Novel Stable Prostacyclin Analogs," *Adv. in Prostaglandin, Thromboxane and Leukotriene Research*, Vol. 11, pp. 267-74 (1983)) ("Aristoff 1983"). Early testing of treprostinil and its alkene parent demonstrated that they did, in fact, retain similar functional properties (*i.e*., inhibition of platelet aggregation, inhibition of thrombosis and vasodilation). *Id*. at 272-73; Aristoff et al, "Synthesis and Structure – Activity Relationships of Benzindene Prostaglandins: Novel Potent Anti-Ulcer Agents," *Adv. in Prostaglandins, Thromboxane and Leukotriene Res.*, Vol. 15, pp. 275-77 (1985)("Aristoff 1985"); Aristoff et al, "Synthesis of Benzindene Prostaglandins: A Novel Potent Class of Prostacyclin Analogs," *Tetrahedron Letters*, Vol. 23, No. 20, pp. 2067-70 (1982) ("Aristoff 1982"); Whittle & Moncada, "Antithrombotic Assessment and Clinical Potential of Prostacyclin Analogues," Chapter 6, Progress in Medicinal Chemistry, Volume 21 (Ellis & West, eds.) pp. 238-279, at p. 238 (1984) ("Whittle 1984"); U.S. Patent No. 4,306,076, to Nelson ("the '076 patent"); Col. 12:27-13:14, Col. 56:15-59-48; Col. 62:5-39. By 1981, it was known that treprostinil was far more stable and had a much longer half-life than prostacyclin. *Id*. It was known that trespostinil was also a potent inhibitor of platelet aggregation and thrombosis and was an effective vasodilator. *See, e.g.*, Whittle 1984; Aristoff 1983 at pp. 272-73; Aristoff 1985 at pp. 275-77; '076 patent. These are the same pharmacological properties that made prostacyclin a suitable and effective agent for treating pulmonary hypertension.

C. The Disclosures and Omissions of the '222 Patent Specification.

The '222 patent specification states that the "present invention is concerned with prostaglandins, specifically benzindene prostaglandins, for use in the treatment or diagnosis of pulmonary hypertension." '222 patent, Col. 1:7-10. The specification further explains that in

cases of primary pulmonary hypertension ("PPH"), life expectancy from time of diagnosis is from 3 to 5 years and death is often sudden. *Id*. at Col. 1:43-58. Applicants state that "[u]ntil now, no successful treatment was known."[4] The specification acknowledges that the benzindene prostaglandins, described in the '075 patent, were effective in inhibiting platelet aggregation and as anti-thrombotic agents. *Id*. Col. 1:60-66. However, the specification states that there "is no indication that these compounds may be used in the treatment of any form of hypertension." *Id*. at Col. 1:66-67. The '222 patent specification claims that the Applicants have "now discovered that within the class of benzindene prostaglandins described in the ['075 patent] there is a sub-class of compounds . . . which are suitable for use in the treatment of pulmonary hypertension." *Id*. at Col. 2:1-5. In fact, the '075 patent expressly disclosed (and indeed claimed) treprostinil, as well as salts thereof, and identified the associated pharmacological properties of anti-platelet aggregation, anti-thrombosis activity, vasodilation and anti-hypertension activity. '075 patent, Col. 14:56-60; 59:33-47; 62:5-39; 74:25-37, Claims 1 and 5. Although the '222 patent specification credited the benzindene prostaglandins disclosed in the '075 patent with having these pharmacological properties, it omits any reference that these same pharmacological properties were known to be effective in the treatment of pulmonary hypertension. '222 patent, Col. 1:60-68.

D. <u>The Prosecution History of the '222 Patent</u>.

The '222 patent claims as originally filed were not limited to treprostinil, but rather encompassed the use of a genus of prostacyclin analogues to treat pulmonary hypertension. The

[4] In fact, it was well known that prostacyclin and certain prostacyclin analogues were effective in treating pulmonary hypertension. *See supra*, Section I(b).

claims that ultimately issued as claims 1 and 2 were added as claims 10 and 11 in a Preliminary Amendment on June 14, 1991.

In an August 1, 1991 Office Action, the Examiner rejected the pending claims as obvious over Aristoff 1985 and Rubin, et al., Circulation, Vol. 66, No. 2, pp. 334-338 (1982)("Rubin"). 8/1/91 Office Action, at p. 3. The Examiner stated that Aristoff "demonstrates the activity of the claimed benzindene prostaglandins as blood pressure depressors," and Rubin "teaches the use of prostacyclin to treat patients with pulmonary hypertension." *Id*. The Examiner further explained that the "claimed subject matter differs from the disclosure of the primary references in claiming specific benzindene prostaglandins for treating pulmonary hypertension," but that the "claimed subject matter would have been obvious given that benzindene prostaglandins are known blood pressure depressors." *Id*. The Examiner concluded that "[a]bsent evidence to the contrary, the benzindene prostaglandins of Rubin are deemed to be equivalent to the benzindene prostaglandins of the claimed invention in their ability to lower pulmonary blood pressure," so the claimed subject matter was deemed obvious. *Id*. at p. 4.

In response to this rejection, Applicants canceled the broader claims directed towards the genus of prostacyclin analogues. The two remaining claims were directed to treatment of pulmonary hypertension using treprostinil or a salt thereof. 2/3/92 Response, at p. 1. Applicants also submitted a declaration by Dr. Walker Long, one of the named inventors, and argued that the claims differed from the cited prior art in that they were directed towards treating pulmonary hypertension, not systemic hypertension. *Id*. at p. 2. Applicants summarized Dr. Long's declaration by explaining that the cited Aristoff reference "teaches that certain benzidine [sic] prostaglandins are capable of lowering blood pressure in rats. The assay which was used to

determine this effect measures changes in systemic blood pressure in rats, not pulmonary blood pressure." *Id*. at pp. 2-3 (emphasis in the original).

In his Declaration dated January 29, 1992, Dr. Long testifies that because the cited Aristoff reference teaches that certain benzindine prostaglandins are capable of lowering systemic blood pressure, not pulmonary blood pressure, the Aristoff reference does not teach that the claimed compounds would be effective in treating pulmonary hypertension. Long Declaration, at pp. 2-3. Dr. Long further stated as follows:

> Furthermore, there is no correlation between the effects of benzidine [sic] prostaglandin compounds on the systemic and pulmonary circulations. In fact, the effects of a given agent on the two circulations are often contradictory. This paradox is especially characteristic of prostaglandin-type compounds. For example, in adult animals the prostaglandin derivatives PGD_2 and PGE_2…vasodilate the systemic circulation (reduce blood pressure) but vasoconstrict the pulmonary circulation and actually cause pulmonary hypertension.

Id. at p. 3.

Dr. Long testified that "[v]ery minor structural differences between prostaglandin derivatives can cause diametrically opposite effects in the systemic and pulmonary circulations, resulting in the complete reversal of a given effect in a given circulation…[c]learly, each prostaglandin compound or analog has unpredictable effects on the pulmonary and systemic circulations." *Id*. at pp. 3-4. Dr. Long explained that Rubin teaches that prostacyclin, "which is a non-benzidindene prostaglandin, reduces pulmonary hypertension." *Id*. at p. 4. Thus, according to Dr. Long, the structural differences between the prior art "non-benzindene prostacyclin" and the claimed "benzindene prostaglandins" are "quite significant," and because "even very minor structural differences between prostaglandin derivatives can lead to completely opposite effects on the pulmonary circulation," one could not predict the effect of the claimed compounds on pulmonary hypertension. *Id*. at pp. 4-5.

Dr. Long further argued that while PGE_2 (figure 2) is "identical to prostacyclin (figure 4) except that it does not possess a double ring structure," the two compounds "have opposite effects on the pulmonary circulation." *Id*. at p. 5. Dr. Long further claimed that both prostacyclin and PGE_2 are "systemic vasodilators," but that prostacyclin is "a pulmonary vasodilator whereas PGE_2 is a pulmonary vasoconstrictor." *Id*. Dr. Long concluded as follows:

> Thus, by knowing the effect of prostacyclin on the pulmonary system, one could not predict the pulmonary effect of related compounds. Since the structures of the benzindene prostaglandin compounds of the present invention are significantly different from prostacyclin…the effect of these compounds on pulmonary pressure could not be predicted by the knowing the effect of prostacyclin on pulmonary pressure."

Id. The Examiner was persuaded by Dr. Long's declaration, withdrew the rejection and issued a Notice of Allowance on April 21, 1992.

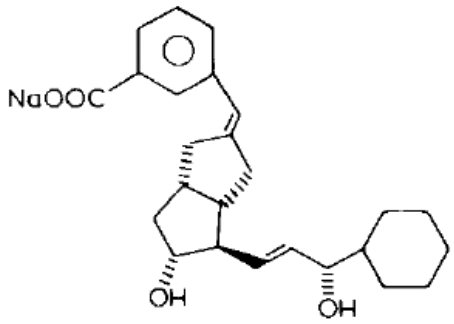
E. The '222 Patent Claims are Invalid as Anticipated

As noted above, prostacyclin, a naturally occurring but unstable metabolite of arachidonic acid was discovered in the 1970s. Whittle 1984. Prostacyclin is synthesized from arachidonic acid and released from cells in the blood vessel wall, and it is "a potent vasodilator and inhibitor of platelet aggregation." Whittle 1984 at p. 238; Aristoff 1983 at p. 267. Prostacyclin plays a vital role in maintaining "vascular tone and haemostasis," and prostacyclin has "many potential clinical applications for the management of thromboembolic and other vascular disorders." *Id*. Notably, the "primary pharmacological activity of prostacyclin presently of major interest to the pharmacologist in the development of their antithrombotic potential is its ability to inhibit platelet aggregation both *in vitro* and *in vivo*." Whittle 1984 at p. 240. Emphasizing the anti-platelet aggregation properties of prostacyclin, Whittle reports that prostacyclin was known as effective in treating pulmonary hypertension. Whittle 1984 at p. 239. Moncada, "The Prostacyclin/Thromboxane Balance And Cardiovascular Disease," *Medicine, 99*

Science and Society, p. 88, 99 (John Wiley & Sons, 1984) ("Moncada 1984") (Prostacyclin is a potent vasodilator in the pulmonary circulation of several species." (p. 88) "Prostacyclin has been used successfully in a few patients with pulmonary hypertension." (p. 99)).

While prostacyclin (also known as epoprostenol and by the trade name Flolan) was available for clinical use by the mid-1980s, administration presented numerous obstacles. Whittle 1984 at p. 239; Aristoff 1983, at p. 267 ("However, the therapeutic utility of PGI_2 is severely limited by the chemical instability of the enol ether, and thus a stable analog should be a much more useful drug."). Prostacyclin is stable in a sodium chloride and glycine buffer solution having a pH of 10.5 for over 24 hours when stored at between 2 and -8 degrees Celsius. Whittle 1984 at p. 239; Moncada 1984, p. 85. Accordingly, prostacyclin was available as a freeze-dried sodium salt and was reconstituted in the above glycine buffer before intravenous administration. Whittle 1984 at p. 239. However, as explained above, there was a strong desire in the field to develop prostacyclin analogues that were more stable, and thus were easier to administer, while retaining the same pharmacologic profile. Whittle 1984 at p. 239; Aristoff 1983 at p. 267.

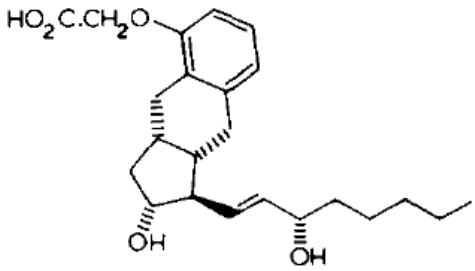
Shortly after the structure of prostacyclin was elucidated, Upjohn Company and Wellcome Research Laboratories began a collaborative study aimed at creating and testing a wide variety of synthetic prostacyclin analogues. Whittle 1984 at p. 239. During this process, an interphenylene analogue of prostacyclin was developed that was shown to be stable, was found to lower blood pressure in rats and was four times less active than prostacyclin. Whittle 1984 at p. 257.



10

Interphenylene

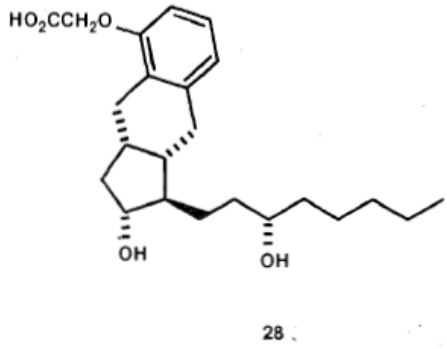
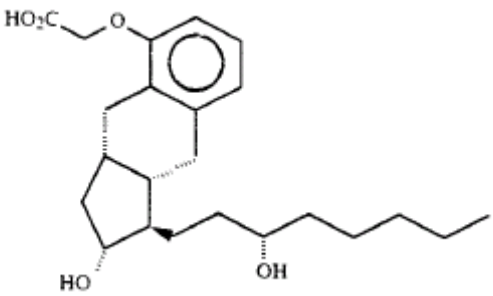
Since it was "known that interphenylene prostaglandins had prostacyclin-like activities," it was hypothesized "that by making the interphenylene derivative of a more conformationally rigid structure by forming a cyclopentane ring, the prostacyclin-like biological profile could be enhanced." Whittle 1984 at p. 257. This endeavor "led to the highly active tricyclic series of stable prostacyclin analogues, the benzindenes." *Id*. A compound identified as "the parent benzindene" was found to be "a potent inhibitor of human platelet aggregation, being 12-times less active than prostacyclin." *Id*.



11

Parent benzindene

The synthesis and biological activity of these benzindene analogues is discussed in more detail in Aristoff 1983. Aristoff 1983 discloses the parent benzindene and the 13,14-dihydrobenzindene analogue, identified as compound 28, among others. Aristoff 1983 at pp. 272-73. A person of ordinary skill in the art at the time of the invention would have understood the 13,14-dihydrobezindene analog disclosed in Aristoff 1983 and shown below to be treprostinil.

	
13,14-Dihydrobezindene	**Treprostinil ('222 patent)**

Compare Aristoff 1983 at pp. 272-73 with '222 patent, Col. 3:1-18.

Treprostinil, as well as other benzindene analogues, is an "extremely potent" inhibitor of platelet aggregation. Aristoff 1983, at p. 273. Compared to PGI_2, which has an ID50 of 2 ng/mL and reduces rat blood pressure response by between 1000-3200 times relative to PGE_1, treprostinil has an ID50 of between 4-20 ng/mL and reduces rat blood pressure by between 100-320 times compared to PGE_1.[5] Aristoff 1983, at p. 273.

1. <u>Aristoff 1983</u>

Aristoff 1983 anticipates claims 1 and 2 of the '222 patent. Those claims are directed methods for treating pulmonary hypertension in a patient, comprising administering to the

patient an effective amount of treprostinil or a salt thereof. '222 patent, claims 1 and 2. Aristoff 1983 discloses treprostinil, as well as its pharmacological properties and therapeutic utility, such as inhibition of platelet aggregation and vasodilation activity. It was known at the time of the invention that these pharmacological properties were effective for treating pulmonary hypertension. Moreover, these pharmacological properties would necessarily have resulted in an effective treatment for pulmonary hypertension. So, although Aristoff 1983 does not specifically reference pulmonary hypertension, the pharmacological properties associated with treprostinil would inherently be effective for treating pulmonary hypertension. Consequently, Aristoff 1983 inherently anticipates claims 1 and 2 of the '222 patent.

Aristoff 1983 starts off by acknowledging the therapeutic utility of prostacyclin by noting that "[i]t is well known that prostacyclin (PGI_2 (Figure 1)) is a powerful vasodilator and extremely potent inhibitor of platelet aggregation." Aristoff 1983 at p. 267. The reference then recognizes the known therapeutic disadvantages of prostacyclin: "The therapeutic utility of PGI_2 is severely limited by the chemical instability of the enol ether, and thus a stable analog should be a much more useful drug." *Id*. To that end, Aristoff states:

> A number of chemically stable analogs have indeed recently been prepared with the 6α-carba derivative 2 (carbacyclin, Fig. 1) looking very promising (1,6). The interphenylene E-type prostaglandins (PGs) 3 (Fig. 1) also appear to show some PGI_2-type activity albeit weak (4). We reasoned that if this class of molecules was interacting at the PGI_2 receptor, then the reactive conformation was not the typical hairpin-type conformation (as shown) but one which more closely resembles the positioning of the upper side chain in prostacyclin or carbacyclin. In particular, if one could somehow fix the conformation of these interphenylene derivatives in such a position, such as shown in 4 (Fig. 1), then perhaps the PGI_2-type activity of these compounds could be enhanced. In this chapter we describe the synthesis and biological

[5] PGE_1 was well known to be a potent vasodilator and inhibitor of platelet aggregation, including in pulmonary vessels and effective in treating pulmonary hypertension. *See* generally Long, "Prostacyclin and Treatment of Pulmonary Hypertension," *Am. Rev. Respir. Dis.*, Vol. 136, pp. 773-75 (1987).

properties of these conformationally rigid interphenylene (i.e., benzindene) analogs.

Id. Aristoff 1983 then depicts the chemical structure of prostacyclin (PGI_2) and its carbacyclin, interphenylene and benzindene analogues:

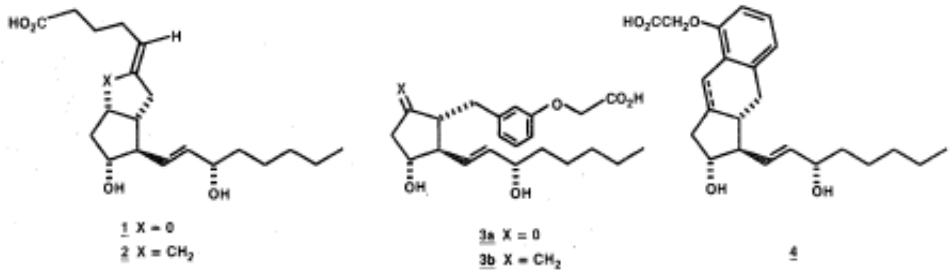
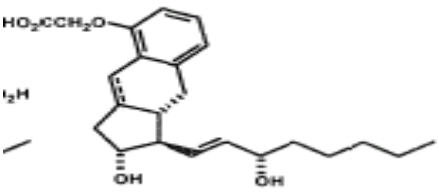
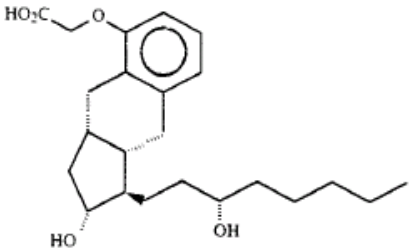
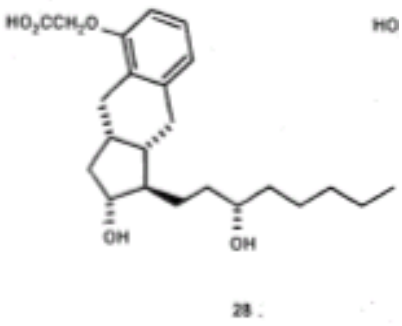
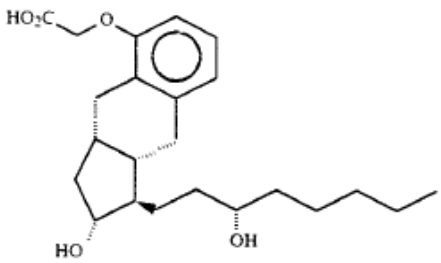


FIG. 1. Structures of PGI_2 (1), carbacyclin (2), interphenylene PGE (3), and benzindene PG (4).

Compound 4 depicted above is the benzindene parent of treprostinil and differs from treprostinil solely by the presence of a double bond instead of a single bond on the omega side chain, as shown below.

 Benzindene Parent Analogue	 Treprostinil Molecule, '222 patent Col. 3

Aristoff further discloses several additional benzindene analogues of prostacyclin, including treprostinil, which is identified as Compound 28. Aristoff 1983 at pp. 269-72.

 Aristoff 1983 Compound 28	 Treprostinil Molecule, '222 patent Col. 3

Aristoff 1983 designates Compound 28 (treprostinil) as the "13,14-dihydrobenzindene analogue." Aristoff 1983 at p. 269.

Aristoff 1983 describes and summarizes the biological activities of the various benzindene analogues, including the 13,14-dihydrobenzindene analogue (Compound 28). Aristoff 1983 at p. 269, 273-74. Aristoff provides a chart summarizing the therapeutic potency of anti-platelet aggregation and blood pressure response (relative to PGE_1, a known vasodilator effective for treating pulmonary hypertension[6]) for several of the prostacyclin analogues, including the 13,14-dihydrobenzindene analogue (treprostinil)).

[6] Long, "Prostacyclin and PGE_1" at p. 773-75.

TABLE 1. *Biological activities*

Compound	ID_{50} (ng/ml)[a]	RBP[b]		
PGI_2 · Na (1)	2	<3200	>1000	↓
16,16-Difluoro (29)	4	<3200	>1000	↓
20-Methyl (30)	5	<320	>100	↓
Parent benzindene (24)	10	<320	>100	↓
13,14-Dihydro (28)	4–20	<320	>100	↓
(6*a*-Carba-PGI_2) (2)	20–40	<320	>100	↓
20-Methyl-15-epi (31)	40–100	<32	>10	↓
(Interphenylene) (3b)	100	<3.2	>1	↓
Benzindene, methyl ester (23)	100–1,000	<320	>100	↓
9-Epi (26)	80–1,000	<32	>10	↓
2′*a*,9-Didehydro (22)	200–1,000	<320	>100	↓
(2′*a*,9),(7,8)-Tetradehydro (25)	1,000	<0.32	>0.10	↓
2*a*-Homo (27)	>1,000	<3.2	>1.0	↓
Para benzindene (20)	>1,000	<1	>0.32	↑

[a] Inhibition of adenosine diphosphate-induced human platelet aggregation (*in vitro*). ID_{50}: PGE_1 = 45 ng/ml.
[b] Rat blood pressure response (*in vivo*) relative to PGE_1 (100 ↓).

Aristoff 1983 characterizes the therapeutic potency of the 13,14-dihydrobenzindene analogue (treprostinil) as follows: "Lower side change analogs such as the 13,14 dihydro . . . compounds are extremely potent inhibitors of platelet aggregation." Aristoff 1983 at p. 273. The reference concludes by stating, "In summary, the benzindene class of prostaglandins represents a novel class of potent PGI_2 (prostacyclin) mimics." *Id*. at p. 274.

In view of the teachings of Aristoff 1983, and, in particular, the disclosure that the 13,14-dihydrobenzindene analogue (treprostinil) was one of the more effective agents in inhibiting platelet aggregation and lowering blood pressure, treprostinil would necessarily have been effective in treating pulmonary hypertension. Consequently, Aristoff inherently anticipates claims 1 and 2 of the '222 patent.[7]

[7] Aristoff 1983 was not cited during prosecution of the '222 patent and was thus never considered by the examiner.

2. Whittle 1984

Whittle 1984 also anticipates claims 1 and 2 of the '222 patent. Whittle 1984 begins by reiterating the common understanding of person of ordinary skill at the time of the claimed invention that prostacyclin had proven therapeutic valuable in patients in preventing platelet aggregation and thrombosis and was thus found to be effective in treating pulmonary hypertension. Whittle 1984, pp. 238-39. Whittle 1984 then explains that "there is much interest in synthesizing a chemically stable analogue which has a biological profile comparable with that of the parent prostacyclin. Furthermore, one of the most important aims of the pharmacologist and chemist working in this area is the definitive separation of the platelet and vascular activities in an orally active synthetic prostacyclin analogue, both for use as a research tool and as a clinically useful agent." Whittle 1984 at p. 239. Whittle explains that the "primary pharmacological activity of prostacyclin presently of major interest to the pharmacologist in the development of their antithrombotic potential is its ability to inhibit platelet aggregation both *in vitro* and *in vivo*." Whittle 1984 at p. 240. Whittle 1984 goes on to analyze several prostacyclin analogues, including several benzindene analogues discussed by Aristoff 1983. Whittle 1984, pp. 246-58. Among these are the benzindene parent analogue and the 13,14-dihydrobenzindene analogue (treprostinil). *Id*. at pp. 254-58.

Whittle 1984 provides *in vitro* results for inhibition of platelet aggregation for several bezindene analogues, including the parent benzindene analogue and 13,14-dihydrobenzindene analogue (treprostinil), as shown below.

Table 6.6. INHIBITION OF ADP-INDUCED HUMAN PLATELET AGGREGATION BY PROSTACYCLIN ANALOGUES *IN VITRO*

Results, given as the IC_{50} value (concentration causing 50% inhibition) following 1 min incubation at 37 °C in PRP and the potency relative to prostacyclin, are the mean ± S.E.M. from at least three experiments.

	IC_{50} (ng ml^{-1})	*Relative potency*
Prostacyclin	0.4 ± 0.1	1
6,9 α-Thiaprostacyclin	19 ± 1	0.02
16,16-Dimethylthiaprostacyclin	825 ± 72	0.0005
9-Deoxy-9α-5-nitrilo-PGF_1	> 2000	< 0.0002
9-Deoxy-9α-6-nitrilo-PGF_1	13 ± 3	0.03
(15*S*)-15-Methylnitrilo-PGF_1	960 ± 50	0.0004
9-Deoxy-6, 9α-imino-PGF_1	> 2000	< 0.0002
5α-5,9α-Epoxy-PGF_1	39 ± 8	0.01
5β-5,9α-Epoxy-PGF_1	310 ± 81	0.01
Δ^2-5α,9α-Epoxy-PGF_1	8 ± 1	0.05
Δ^2-5β,9α-Epoxy-PGF_1	100 ± 25	0.004
5α-13,14-Dihydro-5,9α-Epoxy-PGF_1	92 ± 13	0.004
Δ^2-5α-13,14-Dihydro-5,9α-epoxy-PGF_1	33 ± 5	0.01
Benzindine analogue	7 ± 2	0.06
20-Methylbenzindine	6 ± 0.4	0.07
16,16-Difluorobenzindine	2 ± 0.3	0.2
13,14-Dihydrobenzindine	11 ± 3	0.03

For example, the parent benzindene analogue is disclosed as having a 0.06 relative potency and an Inhibition Concentration[8] of 7 ± 2 ng/mL. Whittle 1984 at p. 254, Table 6.6. The 13,14-dihydrobenzindene analog (treprostinil) is disclosed as having a relative potency of 0.03 when compared with prostacyclin, and an Inhibition Concentration (concentration causing 50% inhibition) of 11 ± 3 ng/mL. Whittle 1984 at p. 254, Table 6.6. A person of ordinary skill in the art at the time of the invention would have understood the 13,14-dihydrobenzindene analogue disclosed in Whittle 1984 to be treprostinil, as explained above. *See* Aristoff 1983, at pp. 272-73.

[8] Inhibition concentration is defined by Whittle 1984 as a value measuring the concentration necessary to cause a 50% inhibition of platelet aggregation. See Whittle 1984, Table 6.6, p. 254.

With respect to benzindene analogues in general, and the 13-14-dihydrobenzindene analog (treprostinil) in particular, Whittle 1984 states as follows:

> It had previously been known that interphenylene prostaglandins had prostacyclin-like activities and it was proposed that by making the interphenylene derivative of a more conformationally rigid structure by forming a cyclopentane ring, the prostacyclin-like biological profile could be enhanced. Such an approach has led to the highly active tricyclic series of stable prostacyclin analogues, the benzindenes. [Citing to Aristoff 1983] In our studies, the parent benzindene (11) was a potent inhibitor of human platelet aggregation, being 12-times less active than prostacylin. (Table 6.6). The 20-methyl benzindene derivative had anti-platelet activity comparable to that of the 16,16-difluoro and 13,14-dihydro deravatives [sic].

Whittle 1984 at pp. 257-58.

Accordingly, a person of ordinary skill in the art at the time of the invention would have understood that Whittle 1984 disclosed treprostinil as having potent anti-platelet aggregation and vasodilation activity similar to prostacyclin, which Whittle 1984 expressly identifies as an agent used to treat pulmonary hypertension. Whittle 1984 discloses the very pharmacological properties of treprostinil (*i.e.*, inhibition of platelet aggregation) that skilled artisans knew made prostacyclin an effective agent for treating pulmonary hypertension and specifically linked those properties to the treatment of that disease. Accordingly, treprostinil as disclosed in Whittle 1984 would necessarily have been effective in treating pulmonary hypertension. Thus, claims 1 and 2 of the ’222 patent are inherently anticipated by Whittle 1984.[9]

3. U.S. Patent No. 4,306,076 to Nelson

The ‘076 patent to Nelson also inherently anticipates the ‘222 patent claims under 35 U.S.C. § 102. The ‘076 patent, issued on December 15, 1981, is entitled Inter-Phenylene CBA Compounds and is generally directed to the disclosure of a large number of prostacyclin

[9] Whittle 1984 was cited during the prosecution of the ‘222 patent. The Examiner, however, did not rely on Whittle 1984 for any purpose during prosecution.

analogues. Among the classes of analogues disclosed are those belonging to the benzindene genus, such as 9-deoxy-2',9-methano (or 2',9-metheno)-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-PGF_1, the parent benzindene analogue to treprostinil. ('076 abstract; Col. 56:16-59:48; Formula XI at Col. 74:30-40).

The '076 patent teaches that the benzindene class of analogues and their salts exhibit prostacyclin-like pharmacological properties including platelet aggregation inhibition, gastric secretion reduction and bronchodilation. '076 patent, Col. 12:27-14:60. Focusing specifically on platelet aggregation inhibition, the '076 patent states as follows:

> In particular, these compounds have useful application as antithrombotic agents . . . These novel CBA analogs disclosed herein are useful whenever it is desired to inhibit platelet aggregation, to reduce the adhesive character of platelets, or to remove or prevent the formation of thrombi in mammals, including man.

'076 patent, Col. 12:35-43. The patent further discloses that the dosage at which this class of benzindene analogues "should be administered to achieve their effect, chiefly anti-platelet aggregation or blood pressure lowering, will vary according to the particular compound under study." '076 patent, Col. 59:33-38. The patent discloses the lowering of blood pressure using a benzindene analogue in a rat. *Id*. at Col. 59:41-45. Finally, as one of the specific benzindene analogues, the '076 patent discloses 9-Deoxy-2',9α-methano-3-oxa-4,5,6-trinor-3,7-(1',3'-inter-phenylene)-13,14-dihydro-PGF_1, which is the chemical name for treprostinil. *See* the '222 patent, claim 1, Example 33, Col. 62:5-39. It also discloses pharmacologically acceptable salts of the prostacyclin analogues. '076 patent, Col. 14:56-60.

In sum, the '076 patent discloses treprostinil and a pharmaceutically acceptable salt thereof as one of the benzindene analogues having "prostacyclin-like" pharmacological properties, including antithrombotic and anti-platelet aggregation functionality. As noted above, skilled artisans at the time of the '222 patent invention would have known that these

pharmacological responses would effectively treat pulmonary hypertension. Further, treprostinil as disclosed in the '076 patent would necessarily be effective for treating pulmonary hypertension. Accordingly, the '076 patent inherently anticipates claims 1 and 2 of the '222 patent.[10]

4. U.S. Patent No. 4,306,075 to Aristoff

The '075 patent to Aristoff also inherently anticipates the '222 patent claims under 35 U.S.C. § 102. The '075 patent, issued on December 15, 1981, is entitled "Composition and Processes" and is generally directed to the disclosure of prostacyclin analogs. The '075 patent discloses various prostacyclin analogues belonging to the benzindene genus, such as 9-deoxy-2',9-methano (or 2',9-metheno)-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-PGF_1, the parent benzindene analogue to treprostinil. '075 abstract; Col. 56:15-59:48; Formula XI at Col. 74:25-35.

The '075 patent discloses that the benzindene class of analogues and their salts exhibit prostacyclin-like pharmacological properties, such as platelet aggregation inhibition, gastric secretion reduction and bronchodilation. '075 patent, Col. 12:27-14:60. With respect to platelet aggregation inhibition in particular, the '075 patent states:

> In particular, these compounds have useful application as antithrombotic agents . . . These novel CBA analogs disclosed herein are useful whenever it is desired to inhibit platelet aggregation, to reduce the adhesive character of platelets, or to remove or prevent the formation of thrombi in mammals, including man.

'075 patent, Col. 12:35-43. The dosage at which this class of benzindene analogues "should be administered to achieve their effect, chiefly anti-platelet aggregation or blood pressure lowering, will vary according to the particular compound under study." '075 patent, Col. 59:33-38.

[10] The '076 patent was not cited during the prosecution of the '222 patent, and, thus, was not considered by the examiner.

Demonstrating the therapeutic utility of these compounds, the '075 patent discloses the lowering of blood pressure using a benzindene analogue in a rat. *Id*. at Col. 59:41-45. Among the specific benzindene analogues the '075 patent discloses is the compound 9-Deoxy-2',9α-methano-3-oxa-4,5,6-trinor-3,7-(1',3'-inter-phenylene)-13,14-dihydro-PGF_1, the chemical name for treprostinil. *See* the '222 patent, claim 1.

The '075 patent discloses treprostinil as one of the benzindene analogues having "prostacyclin-like" pharmacological properties, including antithrombotic and anti-platelet aggregation therapeutic utility. The skilled person at the time of the '222 patent invention knew that these pharmacological properties would effectively treat pulmonary hypertension. Further, treprostinil as disclosed in the '075 patent would necessarily be effective for treating pulmonary hypertension. Accordingly, the '075 patent inherently anticipates claims 1 and 2 of the '222 patent.[11]

F. The '222 Patent Claims are Invalid as Obvious

1. Aristoff 1983, Whittle 1984 and the '076 or '075 patent, either alone or in combination, renders the '222 claims obvious.

As discussed above, prostacyclin was well known to be especially useful in treating pulmonary hypertension because it inhibits platelet aggregation and demonstrates antithrombotic and vasodilation responses. As also noted above, Aristoff 1983, Whittle 1984, the '076 patent and the '075 patent each discloses that treprostinil possesses these very same pharmacological properties and functionalities. (That discussion is incorporated herein by reference). Thus, it would have been obvious to one of ordinary skill in the art at the time of the '222 patent that treprostinil and its salts would also demonstrate effectiveness as a treatment for pulmonary

[11] The '075 patent was disclosed during the prosecution of the '222 patent. The examiner, however, did not rely on the '075 patent in rejecting the claims.

hypertension based on the disclosures of each of Aristoff 1983, Whittle 1984, the '076 patent and the '075 patent, either alone or in combination.

Although Aristoff 1983, the '075 and the '076 patent do not specifically disclose pulmonary hypertension, Whittle 1984 expressly links the pharmacological functionality of treprostinil (*i.e.*, platelet aggregation inhibition and vasodilation) with treating pulmonary hypertension. Whittle 1984 at pp. 238-40. As discussed above in Section II(B), the prior art is riddled with articles and other publications touting the platelet aggregation inhibition and vasodilation properties of prostacyclin and prostacyclin analogues and their consequent potency as treatments for pulmonary hypertension. Moncada & Vane, "The Prostacyclin/Thromboxane Balance and Cardiovascular Disease," *Medicine, Science and Society*, pp. 83-113 (Wiley & Sons 1984); Vane, "Prostaglandins and the Cardiovascular System," *Br. Heart. J.*, Vol. 49, No. 5, pp. 405-09 (1983); Vane, "Adventures and Excursions in Bioassay: The Stepping Stones to Prostacyclin," *Br.J. Pharmac.*, Vol. 79, pp. 821-38 (1983); Moncada & Vane, "The Prostacyclin/Thromboxane Balance and Cardiovascular Disease," *Medicine, Science and Society*, pp. 83-113 (Wiley & Sons 1984); Vane, "Prostaglandins and the Cardiovascular System," *Br. Heart. J.*, Vol. 49, No. 5, pp. 405-09 (1983); Armstrong et al, "Comparison of the Vasodepressor Effects of Prostacyclin and 6-oxo-Prostacyclin F_1 with those of Prostaglandin E_2 in Rats and Rabbits," *Br. J. Pharmac.*, Vol. 62 pp. 125-30 (Jan. 1978); Dusting et al, "Prostacyclin (PGX) is the Endogenus Metabolite Responsible for Relaxation of Coronary Arteries Induced by Arachidonic Acid," *Prostaglandins*, Vol. 13, No. 1, pp. 3-15 (Jan. 1977); Barst, "Pharmacologically Induced Pulmonary Vasodilation in Children and Young Adults with Primary Pulmonary Hypertension," *Chest*, Vol. 86, pp. 497-503 (April 1986); Hanley, "Prostaglandins and the Lung," *Lung*, Vol. 164, pp. 67-77 (1986); Hyman et al, "Prostaglandins

and the Lung," *Am. Review of Resp. Disease*, Vol. 117, pp. 111-36 (1978); Jones, "Treatment of Primary Pulmonary Hypertension with Intravenous Epoprostenol (Prostacyclin)," *Br. Heart J.*, Vol. 57, pp. 270-78 (1978); Long et al, "Prostacyclin and PGE_1 Treatment of Pulmonary Hypertension," *Am. Rev. Respir. Dis.*, Vol. 136, pp. 773-76 (1987).

Because each of Aristoff 1983, Whittle 1984, the '076 patent and the '075 patent are directed to the development of stable analogues of prostacyclin with prostacyclin-like pharmacological responses, it would have been obvious to the skilled artisan to combine the teachings of either Aristoff 1983, the '076 patent or the '075 patent with the disclosures of Whittle or any of the prior art cited in the paragraph above to arrive at treprostinil as an effective treatment for pulmonary hypertension.

Because treprostinil and its pharmaceutically acceptable salts, like prostacyclin, were known to be potent *vasodilators, inhibitors of platelet aggregation, and anti-thrombotic agents*, and because prostacyclin was known to be effective in treating pulmonary hypertension as a result of its anti-platelet, anti-thrombotic and vasodilation properties, one of ordinary skill would have had a reasonable expectation of success of using treprostinil for treating pulmonary hypertension. Use of a known compound with known properties to treat a disease that is known to be impacted by those known properties provides a reasonable expectation of success. There were no unexpected results, because treprostinil performed just as expected and as shown in Aristoff 1983, Whittle 1984, the '075 patent and the '076 patent.

2. Nickolson in combination with Aristoff 1983 or Whittle 1984 renders the claims obvious.

Nickolson discloses that significant efforts were made in the late 1970s and early 1980s to synthesize prostacyclin analogues that would demonstrate the anti-platelet aggregation and vasodilation properties of prostacyclin, while also having a longer half life and greater stability.

Nicolson et al, "Prostacyclin Analogues," *Medicinal Research Rev.*, Vol. 5, No. 1, pp. 1-53 (1985). Nickolson credits prostacyclin as "the most potent natural inhibitor of platelet aggregation." Nickolson at p. 4. Nickolson further explains that prostacyclin has been tested in mammal pulmonary arterial systems and has been found to escape inactivation in the pulmonary arterial system, unlike other prostaglandins. *Id*. at 2, 4. The reference discloses that prostacyclin inhibits platelet aggregation and reduces elevated blood pressures, including pulmonary hypertension. *Id*. at 4-7.

Nickolson recognized that, due to prostacyclin's inherent instability and practical problems involving its clinical use,

> a whole range of structurally-modified prostacyclin analogues have been synthesized since the discovery of PGI_2 with the goal of obtaining chemically *stable* mimics of natural prostacyclin with the *same* or higher biological activity coupled with longer duration of action.

Id. at p. 7 (emphasis in the original). One of ordinary skill at the time of the '222 patent invention would have been motivated to combine the teachings of Nickolson with the disclosures of Aristoff 1983 or Whittle 1984 (both of which disclosed treprostinil and recognized the compound's vasodilation and anti-platelet aggregation properties) to understand that treprostinil would be a prostacyclin analogue with prostacyclin-like vasodilation and anti-platelet aggregation responses suitable for treating pulmonary hypertension. They would have been so motivated to combine the references because each involves the same problem (*i.e.*, finding a more stable alternative to prostacyclin) and the same solutions (*i.e.*, developing stable analogues of prostacyclin which demonstrated similar pharmacological properties). In fact, Nickolson actually cites to Aristoff 1983 as teaching promising prostacyclin analogs, so the motivation to combine is that much more rational.

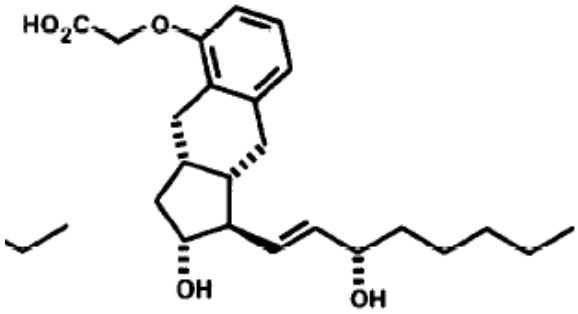
3. Aristoff Total Synthesis or Aristoff 1982 in combination with Rubin 1982 renders the claims obvious.

Aristoff et al., "Total Synthesis of a Novel Antiulcer Agent via a Modification of the Intramolecular Wadsworth-Emmons Wittig Reaction, *J. Amer. Chem. Soc*., Vol. 107, No. 26, p. 7968 (1985) ("Aristoff Total Synthesis") teaches, *inter alia*, the synthesis of benzindene prostaglandins which are chemically stable potent prostacyclin (PGI_2) mimics. As a starting point, Aristoff Total Synthesis teaches "parent compound U-60,959," which the authors describe as "a carbacyclin (1B) type analog (of PGI_2) containing a fused aromatic ring, (and) was about one-fifth as active as PGI_2 at both inhibiting platelet aggregation and lowering blood pressure." Aristoff Total Synthesis at 7967. Further, Aristoff Total Synthesis teaches that further structural modification of the benzindene lower side chain leads to other compounds having beneficial prostaglandin activity. *Id*.

Rubin et al., "Prostaglandin-induced Acute Pulmonary Vasodilation in Primary Pulmonary Hypertension," *American Heart Association, Circulation*, Vol. 66, No. 2, August 1982, pp. 334-338 (1982) ("Rubin") teaches the effects of PGI_2 on pulmonary vascular tone in primary pulmonary hypertension. The authors state that intravenous PGI_2 causes pulmonary vasodilation in animals. Rubin also states that PGI_2 reduced pulmonary vascular resistance in a patient with primary pulmonary hypertension. Further, Rubin established the relationship between reducing pulmonary blood pressure and inhibiting platelet aggregation: "since intra-pulmonary platelet aggregation, as a result of reduced pulmonary blood flow, could further compromise the pulmonary circulation in PPH, the potent pulmonary vasodilator and antiplatelet aggregatory actions of prostacyclin could be benefit in this disease." *Id*. at 334.

Aristoff et al., "Synthesis of Benzindene Prostaglandins: A Novel Potent Class of Stable Prostaglandin Analogs," Tetrahedron Letters, Vol. 23, No. 23, pp. 2067-2070 (1982) ("Aristoff

1982") teaches the same benzindene compound U-60,959 as Aristoff 1985, designated as compound 25 and having the following structure:



25

Aristoff 1982 states that, particularly with respect to "acid 25," that it is a carba-prostaglandin analog (of prostacyclin, PGI_2) with a fused aromatic ring, and that it is twice as active as the carba analog, *i.e.*, 6a-carbaprostaglandin I_2. *Id*. at 2070.

Claims 1-2 of the '222 patent are invalid because they are rendered obvious by the combination of either Aristoff Total Synthesis or Aristoff 1982 and Rubin. Aristoff Total Synthesis and Aristoff 1982 teach benzindene prostaglandin U-60,959, which differs from treprostinil solely by the presence of double C-C bond where treprostinil has a single C-C bond on the omega side chain. Aristoff Total Synthesis and Aristoff 1982 also teach that U-60,959 (or compound 25 in Aristoff 1982) exhibits both inhibition of platelet aggregation and lowering of blood pressure, and Aristoff 1982 further teaches that compound 25 is a potent inhibitor of platelet aggregation and that it is twice as active as the carba analog of prostacyclin. Rubin teaches the relationship between platelet aggregation and pulmonary blood pressure, and teaches that inhibition of platelet aggregation is important in treating pulmonary hypertension. Aristoff Total Synthesis provides motivation for further modification of the sidechain to provide better activity.

Thus, the use of treprostinil for treating pulmonary hypertension would have been obvious to one of skill in the art at the time of the invention based on these references. Such artisan would be motivated, as a further modification of the sidechain of U-60,959, the starting compound, to change the double bond to a single bond and would have a reasonable likelihood of success in obtaining properties similar to or better than those observed with U-60,959. Aristoff Total Synthesis specifically teaches that further structural modifications of the benzindene lower side chain (including removal of the C13-C14 double bond) had additional beneficial pharmacological response. Aristoff Total Synthesis at p. 7967. Aristoff 1985 teaches that the benzindene analogue disclosed in Aristoff Total Synthesis (Compound 3, U-68, 215) which has a single rather than a double bond in the lower side chain demonstrated inhibition of platelet aggregation and changes in blood pressure. Accordingly, the compound thus modified by removing the double bond from U-60,959 would be expected to exhibit both platelet aggregation inhibition and the lowering of pulmonary blood pressure.

G. Secondary Considerations Do Not Mitigate or Negate the Obviousness of the Invention Claimed in the '222 Patent

Once a *prima facie* case of obviousness is established, the burden shifts to the patentee to offer evidence of objective indicia of non-obviousness, such as unexpected results, commercial success, long-felt need, failure of others, and copying. *In re Huang*, 100 F.3d 135, 139 (Fed. Cir. 1996) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)). Although secondary considerations must be considered in an obviousness determination, "they do not necessarily control the obviousness conclusion." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007). The Federal Circuit has held that "evidence of secondary considerations does not always overcome a strong *prima facie* showing of obviousness." *Asyst Technologies, Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008). Additionally, where "the inventions represented no

more than 'the predicable use of prior art elements according to their established functions,' the secondary considerations are inadequate to establish nonobviousness as a matter of law." *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010)(quoting *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 417 (2007)).

Sandoz is unaware of any secondary considerations that negate the obviousness of the inventions of claims 1 and 2 of the '222 patent. It is impossible for Sandoz to anticipate what secondary considerations UTC may rely upon in rebutting Sandoz's obviousness defenses. To the extent that UTC intends to rely on any secondary considerations, much of the evidence concerning such secondary considerations is likely to be in the possession of UTC, and not Sandoz, and UTC has not yet produced any such evidence. Consequently, Sandoz reserves the right to amend its invalidity contentions to address the evidence of alleged secondary considerations that UTC may hereafter produce. Sandoz will also address secondary considerations in its expert disclosures once it has the opportunity to assess UTC's secondary considerations, to the extent it relies on any, and supporting evidence.

1. Long-Felt Need and Failed Attempts by Others

There was no long-felt but unresolved need in 1988 for an effective treatment for pulmonary hypertension. Nor is failed attempts by others a germane consideration in this case. As discussed in detail in Sections II(A) and II(B) above, prostacyclin was developed and known to be an effective treatment for pulmonary hypertension. (These sections are incorporated herein by reference.) See also Whittle 1984 at p. 239; Moncada 1984, pp. 88, 99 (Prostacyclin is a potent vasodilator in the pulmonary circulation of several species." (p. 88) "Prostacyclin has been used successfully in a few patients with pulmonary hypertension." (p. 99).) In fact, prostacyclin was known to be more effective than treprostinil in terms of inhibiting platelet aggregation. Whittle 1984 at p. 254, Table 6.6. Whittle 1984 and Aristoff 1983 also disclose

numerous other prostacyclin analogues having vasodilation and platelet aggregation inhibition responses that may be suitable for treating pulmonary hypertension.

2. Unexpected Results

To prove unexpected results, the patentee must first show what was expected. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007). Then, the patentee must show that the results obtained with the claimed invention, even if superior than what was taught in the prior art, were truly surprising. *Id.* The patentee must show that the results obtained were unexpected as compared with the closest prior art compound. *Pfizer*, 480 F.3d at 1370 (citing *Kao Corp. v. Unilever U. S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006)). In particular, the patentee must show that the claimed invention exhibits unexpected results over the prior art reference supporting the *prima facie* evidence of obviousness. *Aventis Pharma Deutschland GMBH v. Lupin, Ltd.*, 499 F.3d 1293, 1302 (Fed. Cir. 2007).

A showing of unexpected results requires that the results obtained differ "in kind and not merely in degree" when compared with the results obtained with the closest prior art reference. *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004)(quoting *In re Huang*, 100 F.3d 135, 139 (Fed. Cir. 1996)). Thus, the patentee must "produce evidence demonstrating 'substantially improved' results that are unexpected in light of the prior art." *Santarus, Inc. v. Par Pharm., Inc.*, 720 F. Supp. 2d 427, 457 (D. Del. 2010)(quoting *In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995)). Then, any such evidence must be "weighed against contrary evidence indicating that the results were not unexpected or not a substantial improvement over the prior art." *Id.*

As discussed above, treprostinil was known to be a potent inhibitor of platelet aggregation and vasodilator well before the purported invention date of the '222 patent. Sections II(A), (B) and (E) discuss in detail the link between these pharmacological responses and

effective treatments for pulmonary hypertension. (These sections are incorporated herein by reference). Consequently, treprostinil and its salts would have been expected by skilled artisans at the time to be effective for treating pulmonary hypertension. *See e.g.*, Whittle 1984.

3. Commercial Success

UTC has not yet produced any information reflecting sales of Remodulin, market share analysis, or other information from which to assess commercial success. It is Sandoz's belief that prescriptions and unit sales of Flolan and other third-party competitive products outstrip sales of Remodulin as a treatment for pulmonary hypertension. Other competitive products include Iloprost (a prostacyclin analog that is inhaled), Tyvaso (a treprostinil product that is inhaled) and Veletri (an intravenous prostacyclin administered in a buffer having a pH greater than 11). Commercial success cannot be shown where sales of a commercial embodiment of a patent remain low compared to competing products, sales growth has stagnated, and sales fell short of the patentee's expectations. *Santarus, Inc. v. Par Pharm., Inc.*, 720 F. Supp. 2d 427, 453-54 (D. Del. 2010). Moreover, commercial success is not probative if it is merely the result of marketing efforts and promotional offers. *See Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000); *McNeil-PPC, Inc. v. L. Perrigo Co.*, 337 F.3d 1362, 1370 (Fed. Cir. 2003). UTC has not yet produced documents showing its advertising or promotional efforts.

Without the benefit of discovery, Sandoz reasonably believes that the reduced effectiveness of treprostinil compared to prostacyclin (Flolan), the relative failure of treprostinil as a subcutaneous treatment due to pain response by patients, and the higher risk of infection vis-à-vis Flolan has limited and adversely impacted the success of Remodulin in the marketplace.

4. Acclaim and Acknowledgement of Success

Sandoz is unaware that Remodulin has been subject to any measure of acclaim. In fact, Remodulin garnered negative press in 2006-2008 because of reports of higher incidence of infection compared to Flolan. See Section V(A), *infra*.

5. Copying

Copying is not a secondary consideration germane to ANDA litigation. "[A] showing of copying is not compelling evidence of non-obviousness in Hatch-Waxman cases due to the nature of the ANDA process." *Santarus, Inc. v. Par Pharm., Inc.*, 720 F.Supp.2d 427, 458 (D. Del. 2010); *see also Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, 642 F.Supp.2d 329, 373-74 (D. Del. 2009). "[T]he ANDA procedures established by the Hatch-Waxman Act require generic drug manufacturers to copy the approved drug. Variations undermine the FDA's ability to assume that if the patented drug is safe and effective, the generic competitor will also be safe and effective." *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, No. IP 99-38-C H/K, 2001 WL 1397403, at * 14 (S.D. Ind., Oct. 29, 2001). Thus, any evidence of copying is entitled to no probative value, and in any case, cannot overcome Sandoz's strong showing of obviousness.

6. Teaching Away

Teaching away requires an affirmative criticism or disparagement of the claimed invention, and a mere statement that a certain embodiment is preferred or optimal is insufficient. "A reference does not teach away, however, if it merely expresses a general preference of an alternative invention but does not criticize, discredit, or otherwise discourage investigation into the invention claimed." *Depuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009); *see also In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004); *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005). In considering whether a prior art reference teaches away, "all disclosures of the prior art, including unpreferred

embodiments, must be considered." *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989). Sandoz is unaware of any prior art reference that teaches away from using treprostinil for the treatment of pulmonary hypertension. Any such reference, if it exists, must be read in light of the disclosures of Whittle 1984, Aristoff 1983, the '075 patent and the '076 patent, all of which would have encouraged the skilled artisan at the time of the invention to use treprostinil to treat pulmonary hypertension.

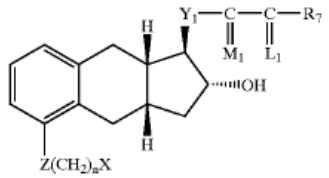
III. CLAIMS 1-4 OF U.S. PATENT No. 6,765,117 ARE INVALID UNDER 35 U.S.C. §§ 102 AND 103

A. Introduction.

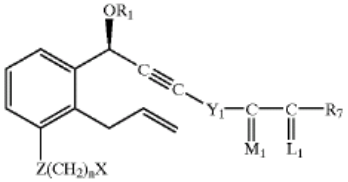
The application resulting in the '117 patent was Application Ser. No. 10/184,907, filed on July 1, 2002 as a division of Application Ser. No. 09/541,521 filed on April 3, 2000, now U.S. Patent No. 6,441,245, which application was a continuation-in-part of Application Ser. No. 09/481,390, filed January 12, 2000, now abandoned, which application was a continuation of Application Ser. No. 08/957,736, filed October 24, 1997, also abandoned. The '117 patent issued on July 20, 2004 and lists Robert M. Moriarty, Raju Penmasta, Liang Guo, Munagala S. Rao and James P. Staszewski as inventors. The patent is assigned to United Therapeutics Corporation on its face. There are four claims in the '117 patent. All of the claims are directed to a compound according to a particular formula "that is produced by a process" as set forth in the particular claim. Claims 1, 3 and 4 are independent; claim 2 depends from claim 1 and claims specific functional groups for Z, X, Y_1, M_1, L_1, R_3, R_4, R_5 and R_7.

Specifically, the claims read as follows:

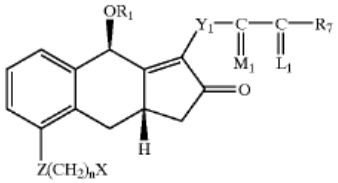
1. A stereoselectively produced isomeric compound according to the following formula:



that is produced by a process for making 9-deoxy-PGF_1-type compounds, the process comprising cyclizing a starting compound of the formula:

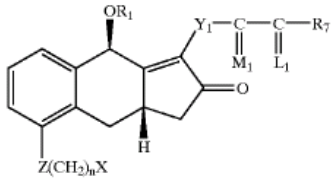


into a compound of the following formula:



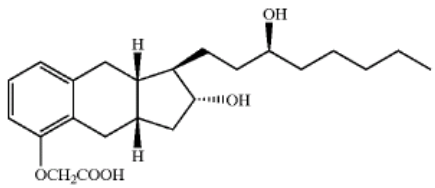
by intramolecular cyclization of the enyne,
wherein
Z is O, S, CH_2, or NR_8 in which R_8 is H, alkyl or aryl;
X is H, CN, OR_9, or $COOR_9$ in which R_9 is H, alkyl, a pharmacologically acceptable cation, THP or TBDMS;
wherein n is 0, 1, 2, or 3;
wherein Y_1 is trans-CH═CH—, cis-CH═CH—, $CH_2(CH_2)_m$-, or —C≡C—; m is 1,2, or 3;

into a compound of the following formula:



by intramolecular cyclization of the enyne,
wherein
Z is O, S, CH_2, or NR_8 in which R_8 is H, alkyl or aryl;
X is H, CN, OR_9, or $COOR_9$ in which R_9 is H;
wherein n is 0, 1, 2, or 3;
wherein Y_1 is trans-CH=CH-, cis-CH=CH-, $-CH_2(CH_2)_m$-, or -C≡C-; m is 1,2, or 3;
wherein R_1 is an alcohol protecting group;
wherein R_7 is
(5) $-C_pH_{2p}-CH_3$, wherein p is an integer from one to 5, inclusive,
(6) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are lydrogen or methyl, being the same or different,
(7) phenyl, bnezyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3)alkoyx, with the proviso that not more than two substituents are other than alkyl,
(8) cis-CH=CH-CH_2-CH_3,
(9) -$(CH_2)_2$-CH(OH)-CH_3, or
(10) -$(CH_2)_3$-CH=C$(CH_3)_2$;
wherein -$C(L_1)$-R_7 taken together is
(11) (C_6-C_7)cycloalkyl optionally substituted by one to 3 (C_1-C_5) alkyl;
(12) 2-(2-furyl)ethyl,
(13) 2-(3-thienyl)ethoxy, or
(14) 3-thienyloxymethyl;
wherein M_1 is α-OH:β-R_5 or α-R_5:β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_1, wherein R_5 is hydrogen or methyl and R_1 is an alcohol protecting group; and
wherein L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro.

4. A steroselectively produced isomeric compound in pharmacologically acceptable salt form according to the following formula:



that is produced by process for making 9-deoxy-PGF_1-type compounds, the process comprising cyclizing a

wherein R_1 is an alcohol protecting group;

wherein R_7 is

(1) —C_2H_{2p}—CH_3, wherein p is an integer from one to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1–C_3)alkyl, or (C_1–C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1–C_3) alkyl, or (C_1–C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl,

(4) cis-CH═CH—CH_2—CH_3,

(5) —$(CH_2)_2$—CH(OH)—CH_3, or

(6) —$(CH_2)_3$—CH═$C(CH_3)_2$;

wherein —$C(L_1)$—R_7 taken together is

(1) (C_4–C_7)cycloalkyl optionally substituted by one to 3 (C_1–C_5) alkyl;

(2) 2-(2-furyl)ethyl,

(3) 2-(3-thienyl)ethoxy, or

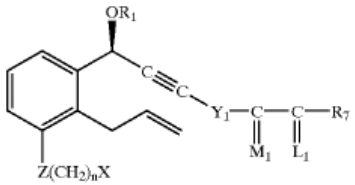
(4) 3-thienyloxymethyl;

wherein M_1 is α-OH:β-R_5 or α-R_5:β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_1, wherein R_5 is hydrogen or methyl and R_1 is an alcohol protecting group; and

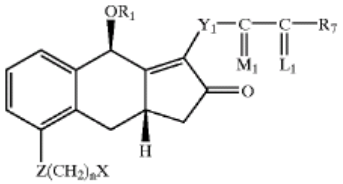
wherein L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro.

2. The stereoselectively produced isomeric compound of claim **1**, wherein Z is O, n is 1, X is COOH, Y_1 is -CH_2CH_2-, M_1 is α-OH:β-R_5, wherein R_5 is hydrogen, L_1 is α-R_3:β-R_4, wherein R_3 and R_4 are hydrogen and R_7 is butyl.

starting compound of the formula:



into a compound of the following formula:



by intramolecular cyclization of the enyne,

wherein

Z is O, S, CH_2, or NR_8 in which R_8 is H, alkyl or aryl;

X is H, CN, OR_9, or $COOR_9$ in which R_9 is a pharmacologically acceptable cation;

wherein n is 0, 1, 2, or 3;

wherein Y_1 is trans-CH=CH-, cis-CH=CH-, -$CH_2(CH_2)_m$-, or -C≡C-; m is 1,2, or 3;

wherein R_1 is an alcohol protecting group;

wherein R_7 is

(1) -C_pH_{2p}-CH_3, wherein p is an integer from one to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,

(3) phenyl ,benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, tow or three chloro, fluoro, tribluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3)alkoyx, with the proviso that not more than two substituents are other than alkyl,

(4) cis-CH=CH-CH_2-CH_3,

(5) -$(CH_2)_2$-CH(OH)-CH_3, or

(6) -$(CH_2)_3$-CH=$C(CH_3)_2$;

wherein -$C(L_1)$-R_7 taken together is

(1) (C_4-C_7)cycloalkyl optionally substituted by one to 3 (C_1-C_5) alkyl;

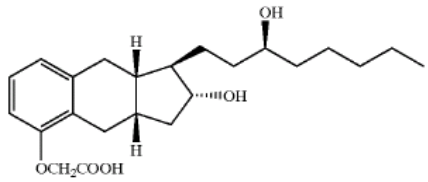
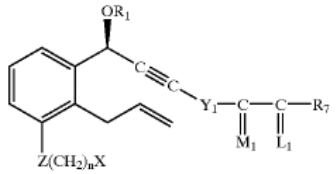
(2) 2-(2-furyl)ethyl,

(3) 2-(3-thienyl)ethoxy, or

(4) 3-thienyloxymethyl;

wherein M_1 is α-OH:β-R_4 or α-R_5:β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_1, wherein R_5 is hydrogen or methyl and R_1 is an alcohol protecting group; and

wherein L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are kydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro.

3. A steroselectively produced isomeric compound according to the following formula:  that is produced by a process for making 9-deoxy-PFG$_1$-type compounds, the process comprising cyclizing a starting compound of the formula:  	

The '117 patent specification states that the "present application relates to a process for producing prostacyclin derivatives and novel intermediate compounds useful in the process". '117 patent, Col. 1:13-16. The '117 patent cites to the '075 patent as prior art that "discloses methods for making prostacyclin derivatives." The '117 patent explains that the invention differs from the prior art in that the "invention relates to a process for preparing 9-deoxy-PGF$_1$-type compounds by a process that is stereoselective and requires fewer steps than the prior art." '117 patent, Col. 4:23-26. The compounds that are produced by the process, however, are known compounds. *See, e.g.*, Abstract, '117 patent at Col. 1:29-4:14.

B. Known Synthetic Routes of Making Prostacyclin Derivatives and Treprostinil.

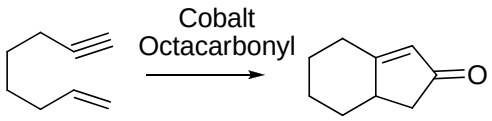
As discussed in the previous section, the '117 patent describes methods of preparing known prostacyclin derivatives. The discussion of the development of prostacyclin analogues and treprostinil provided above in connection with the '222 patent provides a useful background and is relevant here. Accordingly, the discussion of the '222 patent invalidity analysis is reincorporated herein by reference.

As discussed above, treprostinil and its pharmaceutically acceptable salts were known compounds in the art as of the 1980s. See Aristoff 1983, the '075 patent, Whittle 1984, the '076 patent, discussed *supra*. Treprostinil appears to have been first prepared by scientists at the Upjohn Company as part of a program to discover hydrolytically stable prostacyclin analogues. Early preparations resulted in complex mixtures of diasteromers requiring separation and low yields.

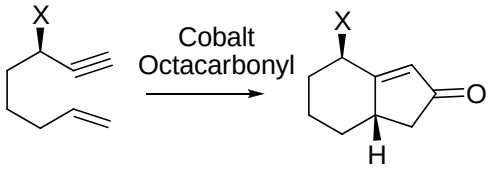
Other early efforts by Upjohn in optimizing the preparation of treprostinil focused on closure strategies for the center ring, which also suffered from lack of sufficient stereocontrol and/or low yields due to lengthy synthetic sequences, such as those disclosed in Aristoff '075. These synthetic procedures were adequate for providing research scale quantities of prostacyclin derivatives but were not adequate for scale-up and manufacturing.

C. <u>The Pauson-Khand Reaction Was Well Known in The Art</u>.

The '117 patent describes the use of the well-known Pauson-Khand chemical reaction to prepare prostacyclin derivatives. The Pauson-Khand reaction was known in the art as of the 1980s. See Mulzer et al, Liebigs.Ann.Chem. 891-897 (1988). The reaction represents a highly reliable route to cyclopentenone intermediates, and its intramolecular variant was well known to exhibit an excellent degree of stereocontrol across a diverse array of structural substrates. See e.g., Schore, N.E. "Transition Metal Alkyne Complexes: Pauson-Khand Reaction," in Comprehensive Organometallic Chemistry II: A review of literature 1982-1994, Vol. 12, Hegedus, L.S. ed. Pergamon, 1995; Brummond, K.M. et al. "Recent Advances in the Pauson-Khand Reaction and Related [2+2+1] Cycloadditions," Tetrahedron 56:3263-3283, (2000). The prototypical intramolecular reaction is as follows:



As of the 1990s the stereodirecting effect of an alpha-propargylic substituent was well established:



good diasteroselectivity

See for example, Mukai et al. Tetrahedron Lett. 1995, 36:5761-5764; Krafft et al. Tetrahedron Lett. 1994, 35:4511-4514; Rowley et al. J. Organomet. Chem. 1991, 413:C5-C9.[12] Indeed, the presence of a propargylic silyl ether was found to be particularly useful in the stereoselective Pauson-Khand reaction (Rowley *supra*). Hence, a person of ordinary skill in the art would have expected the Pauson-Khand reaction to form the rings of prostacyclin derivatives with a high degree of stereoselectivity.

[12] For other examples of stereoselectivity in the Pauson-Khand reaction, see Krafft et al. "The Directed Pauson-Khand Reaction" J. Am. Chem. Soc., Vol. 113, pp. 1693-1703 (1991); Krafft et al. "Regiocontrol in the Intermolecular Cobalt-Catalyzed Olefin-Acetylene Cycloaddtion" J. Am. Chem. Soc., Vol. 110, pp. 968-970 (1988); Krafft et al. "Steric Control in the Pauson Cycloaddition: Further Support for the Proposed Mechanism" Tetrahedron Lett., Vol. 29, pp. 999-1002 (1988); Jamison et al. "Cobalt-Mediated Total Synthesis of (+)-Epoxydictymene" J. Am. Chem. Soc., Vol. 116, pp. 5505-5506 (1994); Yoo et al. "A Total Synthesis of (-)-α-Kainic Acid Involving a Pauson-Khand Reaction as the Key Step" J. Org. Chem., Vol. 59, pp. 6968-6972 (1994); Schore et al. "Diastereofacialselectivity in Intramolecular Pauson-Khand Cycloaddition: Highly Stereoselective Synthesis of Pentalenene" J. Am. Chem. Soc., Vol. 110, pp. 5224-5225 (1988); Rowley et al. "The Pauson-Khand Reaction in Triquinane Synthesis: Approaches to Pentalenene, Pentalenic Acid, and Silphinene" J. Org. Chem., Vol. 57, pp. 6853-6861 (1992); Paquette et al. "Studies Directed Toward the Total Synthesis of Kalmanol. An Approach to Construction of the C/D Diquinane Substructure" J. Org. Chem., Vol. 60, pp. 6912-6921 (1995); Exon et al. "Stereoselectivity of Intramolecular Dicobalt Octacarbonyl Alkene-Alkyne Cyclizations: Short Synthesis of *dl*-Coriolin" J. Am. Chem. Soc., Vol. 105, pp. 2477-2478 (1983); Magnus et al. "Stereospecific Dicobalt Octacarbonyl Mediated Enyne Cyclization for the Synthesis of the Cytotoxic Sequiterpene (+/-)-Quadrone" J. Org. Chem., Vol. 52, pp. 1483-1486 (1987); Magnus et al. "Dicobaltoctacarbonyl-Alkyne Complexes as Intermediates in the Synthesis of Bicyclo[3.3.0]Octenones for the Synthesis of Coriolin and Hirsutic Acid" Tetrahedron, Vol. 41, 5861-5869 (1985); Mulzer et al. "Asymmetric Synthesis of Carbacyclin Precursors by Pauson-Khand Cyclization" Liebigs Ann. Chem., pp. 891-897 (1988).

D. File History of the '117 Patent.

The application that matured to the '117 patent was filed on July 1, 2002. (U.S. Application No. 10/184,907 or "'117 patent application".) The '117 patent application is related to a series of applications including: (1) division of Application Ser. No. 09/541,521 filed on April 3, 2000, now U.S. Patent No. 6,441,245 ("'521 application"); (2) continuation-in-part of Application Ser. No. 09/481,390, filed January 12, 2000, abandoned, ("'390 application"); and (3) continuation of Application Ser. No. 08/957,736, filed October 24, 1997, also abandoned ("'736 application"). See front face of the '117 patent.

The original '736 application contained 9 claims: claims 1-4 were directed to methods of making a 9-deoxy-PGF_1-type compound and claims 5-9 were directed to intermediate compounds which were used in making the 9-deoxy-PGF_1-type compound. On December 16, 1998, Applicants submitted a preliminary amendment canceling original claims 1-9 and adding new claims 10-18, which were directed to methods (claims 10-13) and to intermediate compounds (claims 14-18). 12/16/98 Preliminary Amendment. All of the added claims were rejected in an Office Action dated 6/17/99. Method claim 10 was rejected as an obvious application of the Pauson-Khand reaction to an enyne precursor to give the corresponding cyclopentenone derivative in one step. Intermediate compound claims 14-18 were rejected as unpatentable over the '075 patent.

In response, the Applicants argued that for the method claim there would not have been a reasonable expectation of success for the Pauson-Khand reaction when the enyne was attached to a benzene ring, and that there were no examples of a use of a benzene ring to control the stereochemistry in a Pauson-Khand reaction in the prior art. 9/20/99 Amendment at pp. 5-6. For intermediate compound claims 14-18, Applicant argued that the '075 patent did not render these claims obvious. In particular Applicants stated "[i]t appears that not a single one of these generic

formulas [of the '075 patent] encompasses any compound covered by claims 14-18. *Id.* at p. 6. Based on the representations Applicants made in its 9/20/99 Amendment, the examiner allowed the application. The examiner stated the reasons for allowance that:

> The presently claimed invention teaches a process for making a 9-deoxy-PGF,-type compound employing the Pauson-Khand reaction scheme. The intermediate compounds embraced by claims 14-18 and processes for making them are also novel and unobvious. The closest prior art of record are Mulzer et al, Liebigs.Ann.Chem. 891-897 (1988) and Aristoff, US patent # 4,306,075. Mulzer teaches the Pauson-Khand cyclization of an ene-yne compound to give the corresponding cyclopentenone derivative in one step by reaction with CO,(CO). Mulzer does not teach the process for the compound claimed. Aristoff discloses several prostacyclin compounds but not the compound claimed in claim 18 nor their intermediates claimed in claims 14-17. The process for making these novel compounds are also thus novel.

10/12/99 Notice of Allowance. The Applicants abandoned this application on January 12, 2000.

On the same day Applicants abandoned the original '736 application, Applicants filed the '390 application on January 12, 2000. However, prior to any action on the merits of the '390 application, Applicants abandoned the '390 application on June 2, 2000. Applicants explained in a response to an administrative communication that it paid an extension of time fee because "Applicants needed to maintain pendency [of the '390 application] in order to claim priority based on 35 U.S.C. § 120 in a subsequently filed continuation-in-part application (filed on April 3, 2000)." 5/10/00 Letter. The continuation-in-part application referenced by Applicant in its Letter was the '521 application which was filed on April 3, 2000.

The '521 application included subject matter that was not part of the '736 or '390 applications. The '521 application included, for example, a new description of the starting compounds and intermediate compounds. The new description of the starting compounds and intermediate compounds were included in the claims that were filed with the application. The '521 application was filed with 14 claims. Claims 1-9 were directed to a process for making 9-

deoxy-PGF_1-type compounds and claims 10-14 were directed to the intermediate compounds used in making 9-deoxy-PGF_1-type compounds.

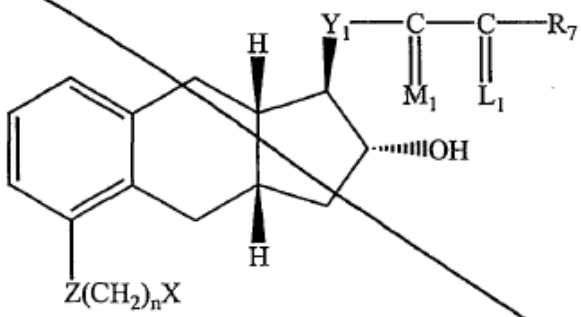
On October 2, 2002, Applicants submitted a preliminary amendment to amend claim 1 and to add new claims 15 and 16. 10/2/00 Preliminary Amendment at pp. 3-4. The examiner thereafter required an election/restriction of the claims on 9/28/01 and Applicants elected claims 1-5 and 14 for prosecution in the '521 application. 9/28/01 Office Action and 10/29/01 Response. The elected claims were eventually allowed in the '521 application and a Notice of Allowance issued on 5/17/02. Thereafter, the '117 patent application was filed on 7/1/02.

When the '117 patent application was filed, Applicants again submitted a preliminary amendment amending claim 1 and adding new claims 15 and 16. 7/1/02 Amendment. Claim 1 was amended to change the following limitation by adding the subject matter that was underlined:

> wherein M_1 is α-OH:β-R_5 or α-R_5:β-OH <u>or α-OR_1:β-R_5 or α-R_5:β-OR_1</u>, wherein R_5 is hydrogen or methyl <u>and R_1 is an alcohol protecting group</u>; and

(underline original) Id at p.6. Added claims 15 and 16 read as follows:

15. (New) A stereoselectively produced isomeric compound according to the following formula:

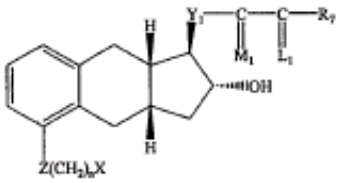


wherein Z, X, Y_1, M_1, L_1, R_7 and n are as defined in claim 1 and said compound is produced according to the stereoselective synthesis of claim 1.

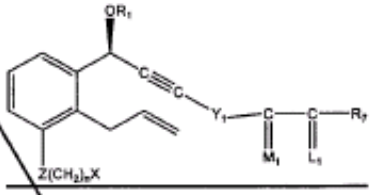
16. (New) The stereoselectively produced isomeric compound of claim 15, wherein Z is O, n is 1, X is COOH, Y_1 is $-CH_2CH_2-$ M_1 is α-OH:β-R_5, wherein R_3 is hydrogen, L_1 is α-R_3:β-R_4, wherein R_3 and R_4 are hydrogen and R_7 is propyl--.

In an Office Action dated April 23, 2003, the Examiner rejected claim 1 under 35 U.S.C. § 112 because the cyclization reaction was claimed generally, while only cobalt-mediated cyclization was disclosed. 4/23/03 Office Action (Sandoz-Trep0002876-80). The examiner also stated that claims 10-13 and 15 and 16 were "drawn to compounds that are free of the prior art" and indicated that these claims were allowable. *Id.* In an Amendment filed October 16, 2003, the Applicants canceled claims 1-14 and incorporated the limitations of claim 1 into allowed claim 15 as follows:

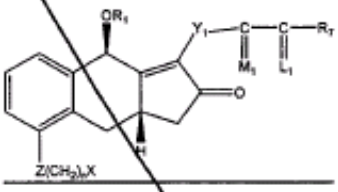
~~18.~~ (Currently amended) A stereoselectively produced isomeric compound according to the following formula:



that is produced by a process for making 9-deoxy-PGF$_1$-type compounds, the process comprising cyclizing a starting compound of the formula:



into a compound of the following formula:



by intramolecular cyclization of the enyne,

wherein

Z is O, S, CH_2, or NR_8 in which R_8 is H, alkyl or aryl;

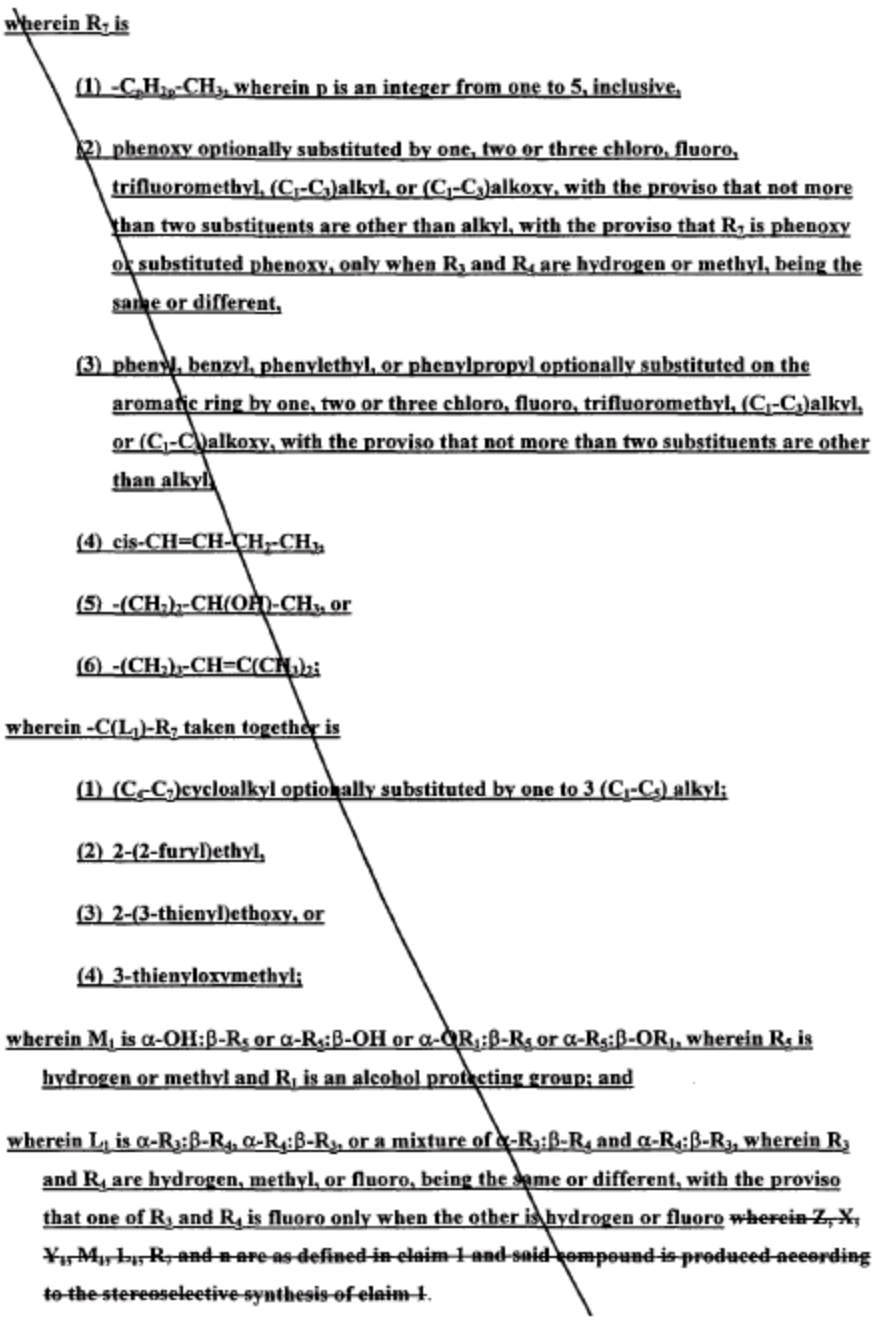
X is H, CN, OR_9, or $COOR_9$ in which R_9 is alkyl, THP or TBDMS;

wherein n is 0, 1, 2, or 3;

wherein Y_1 is trans-CH=CH-, cis-CH=CH-, $-CH_2(CH_2)_m-$, or -C≡C-; m is 1,2, or 3;

wherein R_1 is an alcohol protecting group;

-3-



wherein R_7 is

(1) $-C_pH_{2p}-CH_3$, wherein p is an integer from one to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl,

(4) cis-$CH=CH-CH_2-CH_3$,

(5) $-(CH_2)_2-CH(OH)-CH_3$, or

(6) $-(CH_2)_3-CH=C(CH_3)_2$;

wherein $-C(L_1)-R_7$ taken together is

(1) (C_5-C_7)cycloalkyl optionally substituted by one to 3 (C_1-C_5) alkyl;

(2) 2-(2-furyl)ethyl,

(3) 2-(3-thienyl)ethoxy, or

(4) 3-thienyloxymethyl;

wherein M_1 is α-OH:β-R_5 or α-R_5:β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_1, wherein R_5 is hydrogen or methyl and R_1 is an alcohol protecting group; and

wherein L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro ~~wherein Z, X, Y, M_1, L_1, R_7 and n are as defined in claim 1 and said compound is produced according to the stereoselective synthesis of claim 1~~.

Sandoz-Trep0002886-87.

On November 4, 2003, the examiner issued a Notice of Allowance allowing the only two pending claims in the application, claims 15-16, and stated:

> The following is an examiner's statement of reasons for allowance: the examiner has considered applicants' amendment filed October 9, 2003. In light of said

> amendment, the examiner has withdrawn the rejections of record. The instant claims are drawn to an intermediate prepared during the preparation of 9-deoxy-PGFI-type compounds. The closest prior art of record fails to teach or fairly suggest the claimed intermediate. As such, the instant claims are allowed.

11/4/03 Notice of Allowance.

Rather than pay the issue fee and allow the application to pass to issue after the Notice of Allowance, the Applicants filed a Request for Continued Examination (RCE) and another amendment. 12/3/03 RCE and Amendment. The Amendment directed the addition of approximately three columns of text to the background section of the original application. In particular, the amendment added the text that is shown between column 1, lines 29 to column 4, line 14 of the '117 patent. *Id.* The Applicant explained the amendments to the specification by stating:

> The amendments to the specification on page 1 provide material from U.S. Patent No. 4,306,075, which is referenced on page 1, line 14 [now column 4, line 15 of the '117 patent] and was incorporated by reference in its entirety as per the concluding paragraph on page 19 of the specification [now column 21, lines 18-21 of the '117 patent]. The added material reflects the types of compounds which were prepared by the prior art process (see col. 3, line 19-col. 5, line 30) and defines the type of moieties encompassed by –COOR1 (see col. 14, line 44-col. 15, line 29). The present process is directed to the preparation of the same type of compounds albeit with a shorter stereoselective synthetic method. The present process provides these compounds referred to in the '075 patent as CBA analogs as steroselective [sic] produced isomeric prostacyclin compounds.

12/3/03 Amendment at p. 14 (Sandoz-Trep 0002904-18 at Sandoz-Trep 0002917).

The amendment also amended the claims. Claim 15 was amended to recite that R_9 can be "H" or "a pharmacologically acceptable cation;" claim 16 was amended to recite that R_7 is "butyl" rather than "propyl;" and claims 17-18 were newly added. *Id.* The examiner issued another Notice of Allowance on February 17, 2004 and stated among the reasons for allowance that "[n]o new prior art has been found to negate the patentability of the instant claims, and as such, the instant claims are allowed for the same reasons set forth in Paper No. 7 [11/4/03 Notice

of Allowance, *supra*]." Claims 15-18 were renumbered and issued as claims 1-4 in the '117 patent.

E. The '117 Patent Claims are Invalid as Anticipated

1. U.S. Patent No. 4,306,075 to Aristoff

Claims 1-4 of the '117 patent are invalid as anticipated under 35 U.S.C. § 102(b) by the '075 patent. As discussed above, claims 1-4 are directed to a compound "that is produced by a process for making" the compound. These claims are in a form known as "product-by-process" claims. *Atlantic Thermoplastics Co. v. Faytex Corp.*, 970 F.2d 834, 842 (Fed. Cir. 1992) citing *Chisum, Patents* § 8.05 (1991) ("A 'product-by-process' claim is one in which the product is defined at least in part in terms of the method or process by which it is made."); *Cf. Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1291 (Fed. Cir. 2009)(en banc).

"In determining validity of a product-by-process claim, the focus is on the product and not on the process of making it." *Amgen Inc. v. F. Hoffmann-La Roche, Ltd.*, 580 F.3d 1340, 1369 (Fed. Cir. 2009) citing *Atl. Thermoplastics Co. v. Faytex Corp.*, 970 F.2d 834, 841 (Fed. Cir. 1992); *Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1292 (Fed. Cir. 2009)(en banc) citing *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) (". . . even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself").

A product-by-process claim is invalid as anticipated if the product is anticipated. *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1317 (Fed. Cir. 2006) ("It has long been established that one cannot avoid anticipation by an earlier product disclosure by claiming the same product . . . as produced by a particular process."); *Amgen Inc. v. F. Hoffmann-La Roche, Ltd.*, 580 F.3d 1340, 1366 (Fed. Cir. 2009)("It has long been the case that an old product is not patentable even if it is made by a new process."); see also *Gen. Elec. Co. v. Wabash*

Appliance Corp., 304 U.S. 364, 373, 58 S. Ct. 899, 82 L. Ed. 1402, 1938 Dec. Comm'r Pat. 813 (1938) ("[A] patentee who does not distinguish his product from what is old except by reference, express or constructive, to the process by which he produced it, cannot secure a monopoly on the product by whatever means produced."); *Cochrane v. Badische Anilin & Soda Fabrik*, 111 U.S. 293, 311, 4 S. Ct. 455, 28 L. Ed. 433, 1884 Dec. Comm'r Pat. 230 (1884) ("While a new process for producing [the product] was patentable, the product itself could not be patented even though it was a product made [by an artificial process] for the first time.").

The *SmithKline Beecham Corp. v. Apotex Corp* case is particularly instructive on the standard for anticipation of product-by-process claims. In *SmithKline*, the Federal Circuit held that product-by-process claims drawn to a known compound were anticipated by prior disclosure of that compound, even though the claims recited a different method of making the compound. *Id.* at 1317. The Federal Circuit explained the rationale behind its holding as follows:

> Regardless of how broadly or narrowly one construes a product-by-process claim, it is clear that such claims are always to a product, not a process. It has long been established that one cannot avoid anticipation by an earlier product disclosure by claiming the same product more narrowly, that is, by claiming the product as produced by a particular process.

Id.

As explained above, the patentee originally filed process claims in the '117 patent application, e.g., claims 1-9, as well as claims directed to the intermediate compounds per se, e.g., 10-14. However, the Applicant added product-by-process claims 15-18 to the '117 patent application by amendment. The main process claim was rejected as not enabled but the intermediate compound claims, e.g., claims 10-13, were indicated as allowable. See 4/23/03 Office Action (Sandoz-Trep0002876-80). Instead of pursuing either of the pure process claims

or the pure compound claims, the Applicants decided to pursue product-by-process claims 15-18, now claims 1-4 in the '117 patent.

Further, the products produced in the product-by-process of claims 1-4 were admittedly known in the art. During prosecution of the '117 patent application, the Applicants admitted that the processes disclosed in the '117 patent application were "directed to the preparation of the same type of compounds" disclosed in the '075 patent. *See* 12/3/03 Amendment at p. 14 (Sandoz-Trep 0002904-18 at Sandoz-Trep 0002917). Hence, claims 1-4 of the '117 patent are anticipated by the '075 patent.

2. Prior Art that Discloses Treprostinil

As explained in the preceding section, claims 1-4 are product-by-process claims. The validity of such claims turns on whether the products covered by the claims are anticipated or obvious. To the extent that claims 1-4 cover treprostinil or a pharmaceutically acceptable salt thereof produced by the process, the claims are anticipated by all prior art that disclose treprostinil and its pharmaceutically acceptable salts. These prior art references include the '222 patent, Aristoff 1983, Whittle 1984, the '076 patent, the '075 patent, all discussed above.

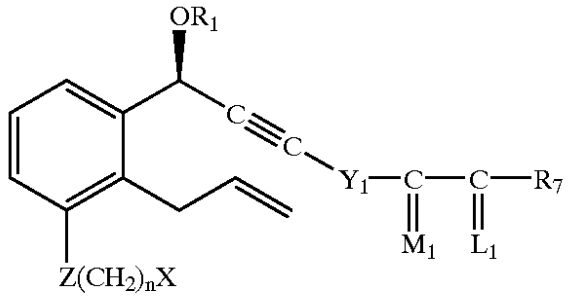
3. WO 99/21830 to Moriarty

Claims 1-4 of the '117 patent are invalid as anticipated under 35 U.S.C. § 102(b) by the international patent application of WO 99/21830 to Moriarty (Moriarty '830). Moriarty '830 was published on May 6, 1999 and is prior art to the '117 patent under 35 U.S.C. § 102(b) since the effective filing date of the '117 patent is July 1, 2002, the date that the'117 patent was filed.

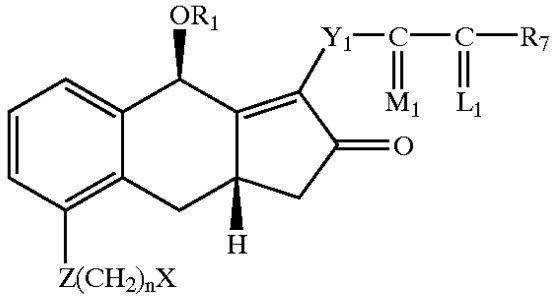
Although the '117 patent claims the benefit of earlier filed applications, none of the claims of the '117 patent are entitled to a filing date of any earlier filed application because none of the claims are supported by any earlier application pursuant to 35 U.S.C. § 120. See *Studiengesellschaft Kohle m.b.H. v. Shell Oil Co.*, 112 F.3d 1561, 1564 (Fed. Cir. 1997)("To

qualify for an earlier filing date, section 120 requires, inter alia, that the earlier-filed U.S. patent application contain a disclosure which complies with 35 U.S.C. § 112, P 1 (1994) for each claim in the newly filed application. Thus, this benefit only applies to claims that recite subject matter adequately described in an earlier application, and does not extend to claims with subject matter outside the description in the earlier application.").

Claims 1-4 of the '117 patent are not supported by the divisional application (the '521 application) to which it claims priority.[13] As explained above, claims 1-4 are product-by-process claims. Each claim contains the limitation that the process comprises cyclizing a starting compound of formula:



into a compound of the following formula



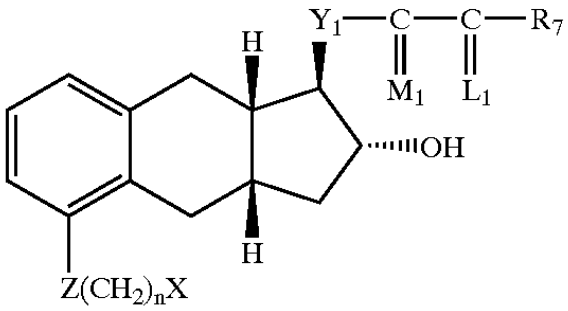
[13] In addition, since the '117 patent is not entitled to the benefit of the filing date of the '521 divisional application, it is not entitled to the benefit of the filing dates of the continuation-in-part application No. 09/481,390 or the continuation application No. 08/957,736 since both of these applications were not pending when the '117 application was filed. See 35 U.S.C. § 120. Even assuming, arguendo, that the other applications in the chain of

(continued…)

by intramolecular cyclization of the enyne.

Claims 1, 3, and 4 each contain the further limitation that "M_1 is . . . α-OR_1:β-R_5 or α-R_5:β-OR_1, wherein…R_1 is an alcohol protecting group". This limitation was added to claims 1, 3 and 4 during prosecution of the '117 patent application. The '521 application, to which the '117 patent claims priority, does not disclose this claim limitation. While there are specific structures shown in the '521 application where R_1 is an alcohol protecting group, there is no disclosure or examples which describe or illustrate M_1 as being α-OR_1:β-R_5 or α-R_5:β-OR_1, wherein R_5 is methyl and R_1 is an alcohol protecting group.

In addition, claims 1, 2, and 3 lack written support for wherein R_9 is "H" or X is "COOH"; claims 1 and 4 lack written support for wherein R_9 is "a pharmacologically acceptable cation"; claim 4 lacks written support for the term "in pharmacologically acceptable salt form"; claim 2 also lacks written support for the starting compound having the groups recited in claim 2; and claims 1 and 2 lack written support for the formula



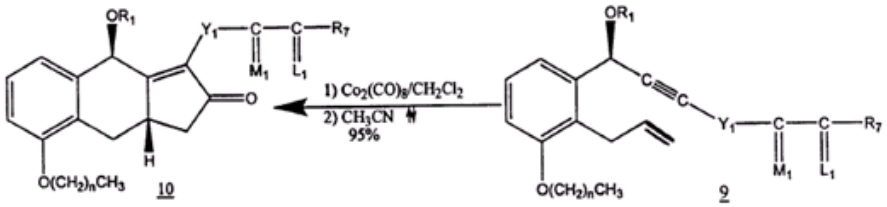
All of the foregoing terms and claims were added to the '117 patent application during prosecution of the '117 patent application and none of the claims are supported by the '521 divisional application. Thus, the '117 patent is not entitled to the benefit of the filing date of the

priority were eligible for consideration, they also lack written descriptive support for claims 1-4 for the same reasons identified for the '521 divisional application.

'521 application because it does not provide written support for the subject matter of claims 1-4 of the '117 patent under 35 U.S.C. § 112. See 35 U.S.C. § 120; *Studiengesellschaft Kohle m.b.H. v. Shell Oil Co.*, 112 F.3d 1561, 1564 (Fed. Cir. 1997). Accordingly, claims 1-4 of the '117 patent have an effective date that is the same date that application for the '117 patent was filed, which is July 1, 2002.

Moriarty '830 anticipates each claim of the '117 patent. The international patent application, WO 99/21830 to Moriarty (Moriarty '830), was published on May 6, 1999. Since the effective filing date of claims 1-4 of the '117 patent is July 1, 2002, Moriarty '830 is prior art under 35 U.S.C. § 102(b). Moriarty '830 discloses and claims a sub-set of the compounds and processes claimed in the '117 patent and thereby anticipates claims 1-4 of the '117 patent. In particular, Moriarty '830 discloses the following sub-set of compounds:

In one embodiment, the present invention relates to an improved stereoselective method for making 9-deoxy-PGF_1-type compounds comprising the following reaction:



wherein n is 0, 1, 2, or 3;

wherein Y_1 is trans-CH=CH-, cis-CH=CH-, $-CH_2(CH_2)_m-$, or -C≡C-; m is 1,2, or 3;

wherein R1 is an alcohol protecting group;

wherein R_7 is

(1) $-C_pH_{2p}-CH_3$, wherein p is an integer from one to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl,

(4) cis-CH=CH-CH_2-CH_3,

(5) -$(CH_2)_2$-CH(OH)-CH_3, or

(6) -$(CH_2)_3$-CH=$C(CH_3)_2$;

wherein -$C(L_1)$-R_7 taken together is

(1) (C_4-C_7)cycloalkyl optionally substituted by one to 3 (C_1-C_5) alkyl;

(2) 2-(2-furyl)ethyl,

(3) 2-(3-thienyl)ethoxy, or

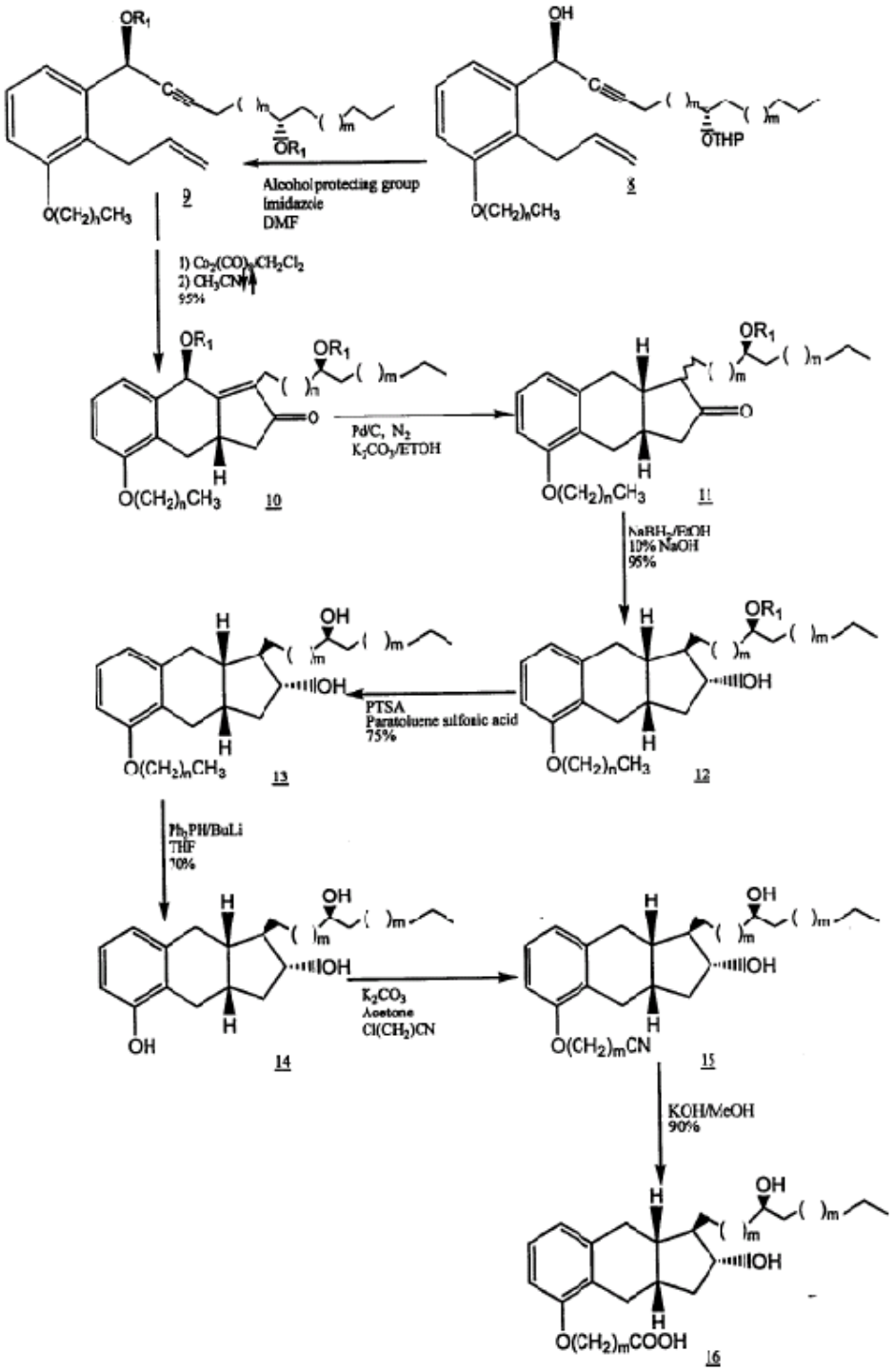
(4) 3-thienyloxymethyl;

wherein M_1 is α-OH:β-R_5 or α-R_5:β-OH, wherein R_5 is hydrogen or methyl;

wherein L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro.

Moriarty ‘830 at pp. 2-3.

Further, Moriarty ‘830 discloses the following synthesis at pages 4-5:



The above disclosure anticipates every element of claims 1-4 of the '117 patent. In particular, with respect to claim 1, Moriarty '830 discloses a species within the claimed genus with respect to the starting compound, intermediate compound, and ending compound. The

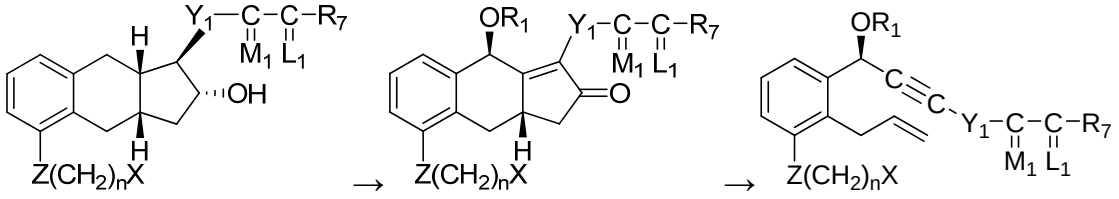
synthesis in Moriarty '830 involves cyclization of the eyne. With respect to claims 2-4 of the '117 patent, Moriarty '830 discloses the species claimed in each of these three claims as well as the claimed cyclization step.

F. The '117 Patent Claims are Invalid as Obvious

As explained above, claims 1-4 are product-by-process claims. To the extent that claims 1-4 cover treprostinil or a pharmaceutically acceptable salt thereof produced by a process, the claims are obvious over the prior art.

As discussed in the above subsections of Section III and in the '222 patent sections, treprostinil, its salts and processes for their production were known. The Pauson-Khand reaction was also widely known. See Section III(C) above. A person of ordinary skill in the art at the time of the invention would have been motivated to modify the prior art processes of making treprostinil and its salts by using the known Pauson-Khand reaction with a reasonable expectation of success.

For example, the Pauson-Khand disconnect shown below is a readily envisioned pathway that would have been obvious to the skilled artisan.



Treprostinil Enone Adduct Pauson-Khand Substrate

Access to the requisite enantiomerically pure propargylic alcohol would have been well known and numerous methodologies were available prior to the time of filing including, for example, the Corey-Bakshi-Shibata (CBS) reduction (Corey et al. Tetrahedron Lett. 1995, 36:9153-9156). Employing a silyl ether (OR_1 in Pauson-Khand Substrate and Enone Adduct) as the

stereodirecting functional group, as taught by Rowley et al., would have provided the expected stereochemistry at C9 upon which all other centers would be subsequently controlled. The cyclization models disclosed in Shore (*Shore at 724-726*) showing a mechanistic rationale for stereocontrol in the Pauson-Khand reaction would have provided the skilled artisan with a reasonable expectation of success. Thus claims 1-4 would have been rendered obvious in view of Schore in view of Rowley and in further view of Corey.

G. Secondary Considerations Do Not Mitigate or Negate the Obviousness of the Invention Claimed in the '117 Patent

UTC bears the burden of providing evidence of objective indicia of non-obviousness. *In re Huang*, 100 F.3d 135, 139 (Fed. Cir. 1996) "Evidence of secondary considerations does not always overcome a strong *prima facie* showing of obviousness." *Asyst Technologies, Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008); *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010); *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 417 (2007)).

Sandoz is unaware of any secondary considerations that negate the obviousness of the inventions of the asserted claims of the '117 patent. It is impossible for Sandoz to anticipate what secondary considerations UTC may rely upon in rebutting Sandoz's obviousness defenses. To the extent that UTC intends to rely on any secondary considerations, much of the evidence concerning such secondary considerations is likely to be in the possession of UTC, and not Sandoz, and UTC has not yet produced any such evidence. Consequently, Sandoz reserves the right to amend its invalidity contentions to address the evidence of alleged secondary considerations that UTC may hereafter produce. Sandoz will also address secondary considerations in its expert disclosures once it has the opportunity to assess UTC's secondary considerations, to the extent it relies on any, and supporting evidence.

1. Long-Felt Need and Failed Attempts by Others

There is no evidence of a long-felt need or failed attempts by others with respect to the claimed inventions of the '117 patent. As explained in sections III.E and III.F above, the compounds produced by the processes of the claims were well known and the Pauson-Khand reaction used in the processes of the claims was also widely known prior to the invention of the '117 patent.

2. Unexpected Results

To prove unexpected results, the patentee must first show what was expected. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007). Then, the patentee must show that the results obtained with the claimed invention, even if superior than what was taught in the prior art, were truly surprising. *Id.* The patentee must show that the results obtained were unexpected as compared with the closest prior art compound. *Pfizer*, 480 F.3d at 1370 (citing *Kao Corp. v. Unilever U. S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006)). In particular, the patentee must show that the claimed invention exhibits unexpected results over the prior art reference supporting the *prima facie* evidence of obviousness. *Aventis Pharma Deutschland GMBH v. Lupin, Ltd.*, 499 F.3d 1293, 1302 (Fed. Cir. 2007).

A showing of unexpected results requires that the results obtained differ "in kind and not merely in degree" when compared with the results obtained with the closest prior art reference. *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004)(quoting *In re Huang*, 100 F.3d 135, 139 (Fed. Cir. 1996)). Thus, the patentee must "produce evidence demonstrating 'substantially improved' results that are unexpected in light of the prior art." *Santarus, Inc. v. Par Pharm., Inc.*, 720 F. Supp. 2d 427, 457 (D. Del. 2010)(quoting *In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995)). Then, any such evidence must be "weighed against contrary

evidence indicating that the results were not unexpected or not a substantial improvement over the prior art." *Id.*

As explained in section III.C above, the process limitations of the '117 patent claims involve the Pauson-Khand reaction. This reaction was known in the art as of the 1980s and was also known to be a highly reliable route to forming the cyclopentenone intermediates shown in the claims. The Pauson-Khand reaction was also well known to exhibit an excellent degree of stereocontrol across a diverse array of structural substrates. Consequently, the products produced according to the claimed processes and the claimed processes themselves act as a person of skill in the art would have expected.

3. Commercial Success

UTC has not produced evidence to suggest that its Remodulin product embodies the product by process claimed in the '117 patent claims. UTC has also not yet produced any information reflecting sales of Remodulin, market share analysis, or other information from which to assess commercial success. It is Sandoz's belief that prescriptions and unit sales of Flolan and other third-party competitive products outstrip sales of treprostinil as a treatment for pulmonary hypertension. Other competitive products include Iloprost (a prostacyclin analog that is inhaled), Tyvaso (a treprostinil product that is inhaled) and Veletri (an intravenous prostacyclin administered in a buffer having a pH greater than 11). Commercial success cannot be shown where sales of a commercial embodiment of a patent remain low compared to competing products, sales growth has stagnated, and sales fell short of the patentee's expectations. *Santarus, Inc. v. Par Pharm., Inc.*, 720 F. Supp. 2d 427, 453-54 (D. Del. 2010). Moreover, commercial success is not probative if it is merely the result of marketing efforts and promotional offers. *See Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d

1120, 1130 (Fed. Cir. 2000); *McNeil-PPC, Inc. v. L. Perrigo Co.*, 337 F.3d 1362, 1370 (Fed. Cir. 2003). UTC has not yet produced documents showing its advertising or promotional efforts.

Without the benefit of discovery, Sandoz reasonably believes that the reduced effectiveness of treprostinil compared to prostacyclin (Flolan), the relative failure of treprostinil as a subcutaneous treatment due to pain response by patients, and the higher risk of infection vis-à-vis Flolan has limited and adversely impacted the success of Remodulin in the marketplace.

There is also no link between any sales success of Remodulin and the claimed manufacturing process claimed in the '117 patent claims. Commercial success is probative of non-obviousness "only if here is proof that the sales were a direct result of the unique characteristics of the claimed invention—as opposed to other economic and commercial factors unrelated to the quality of the patented subject matter." *In re Huang*, 100 F.3d at 140. Further, the commercial success must be "attributable to something disclosed in the patent that was not readily available in the prior art." *J.T. Eaton & Co., Inc. v. Atlantic Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997). Thus, commercial success is not probative of non-obviousness if the success "was due to unclaimed or non-novel features of the [claimed invention]". *Ormco Corp. v. Align Technology, Inc.*, 463 F.3d 1299k, 1312 (Fed. Cir. 2006). Moreover, commercial success must be due to "the subject matter that [the patentee] contends is nonobvious." *Friskit, Inc. v. Realnetworks, Inc.*, 306 F.3d Appx. 610, 617 (Fed. Cir. 2009). Here, there is no evidence that any purported commercial success achieved by Remodulin was due to any novel features of the manufacturing process identified in the '117 patent claims.

4. <u>Acclaim and Acknowledgement of Success</u>

Sandoz is unaware that Remodulin has been subject to any measure of acclaim. In fact, Remodulin garnered negative press in 2006-2008 because of reports of higher incidence of infection compared to Flolan. See Section V(A), *infra*.

5. Copying

Copying is not a secondary consideration germane to ANDA litigation. "[A] showing of copying is not compelling evidence of non-obviousness in Hatch-Waxman cases due to the nature of the ANDA process." *Santarus, Inc. v. Par Pharm., Inc.*, 720 F.Supp.2d 427, 458 (D. Del. 2010); *see also Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, 642 F.Supp.2d 329, 373-74 (D. Del. 2009). "[T]he ANDA procedures established by the Hatch-Waxman Act require generic drug manufacturers to copy the approved drug. Variations undermine the FDA's ability to assume that if the patented drug is safe and effective, the generic competitor will also be safe and effective." *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, No. IP 99-38-C H/K, 2001 WL 1397403, at * 14 (S.D. Ind., Oct. 29, 2001). Thus, any evidence of copying is entitled to no probative value, and in any case, cannot overcome Sandoz's strong showing of obviousness.

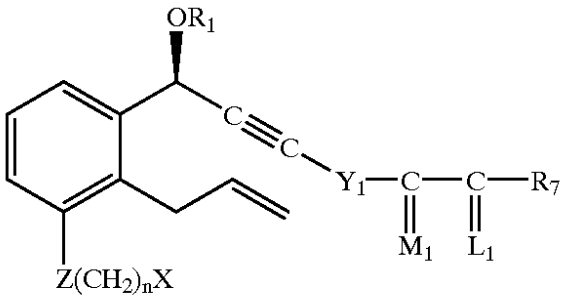
6. Teaching Away

Teaching away requires an affirmative criticism or disparagement of the claimed invention, and a mere statement that a certain embodiment is preferred or optimal is insufficient. "A reference does not teach away, however, if it merely expresses a general preference of an alternative invention but does not criticize, discredit, or otherwise discourage investigation into the invention claimed." *Depuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009); *see also In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004); *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005). In considering whether a prior art reference teaches away, "all disclosures of the prior art, including unpreferred embodiments, must be considered." *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989). Sandoz is unaware of any prior art reference that teaches away from using the features of the manufacturing process identified in the product by process claims of the '117 patent, including the use of the starting or intermediate compounds recited in the claims.

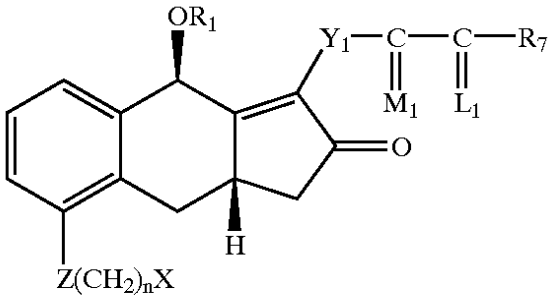
IV. THE '117 PATENT CLAIMS ARE INVALID UNDER 35 U.S.C. § 112(1)

The specification of the '117 patent does not provide a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains. In particular, the specification lacks a written description for the subject matter of claim 1-4. The test for compliance with the written description requirement is whether the disclosure of the application reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010)(en banc).

As explained above, claims 1-4 are product-by-process claims. Each claim contains the limitation that the process comprises cyclizing a starting compound of formula:



into a compound of the following formula

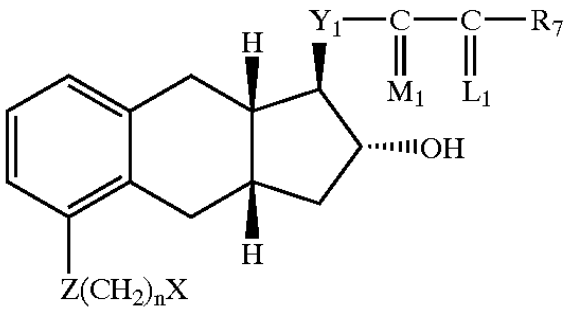


by intramolecular cyclization of the enyne.

Claims 1, 3, and 4 each contain the further limitation that "M_1 is . . . α-OR_1:β-R_5 or α-R_5:β-OR_1, wherein R_5 is hydrogen or methyl and R_1 is an alcohol protecting group". This limitation was added to claims 1, 3 and 4 during prosecution of the '117 patent application.

However, there is no general or specific disclosure of this term anywhere in the '117 patent application. While there are specific structures shown where R_1 is an alcohol protecting group, there is no disclosure or examples which describe or illustrate M_1 is α-OR_1:β-R_5 or α-R_5:β-OR_1, wherein R_5 is methyl and R_1 is an alcohol protecting group. Hence, the '117 patent does not provide written support for claims 1, 3 and 4 pursuant to 35 U.S.C. § 112.

In addition, claims 1, 2, and 3 lack written support for wherein R_9 is "H" or X is "COOH"; claims 1 and 4 lack written support for wherein R_9 is "a pharmacologically acceptable cation"; claim 4 lacks written support for the term "in pharmacologically acceptable salt form"; and claims 1 and 2 lack written support for the formula



All of the foregoing terms and claims were added to the '117 patent application during prosecution of the application and none of the claims are supported by the original disclosure.

Further, claim 2 also lacks written support for the starting compound having the recited groups. Although the compounds disclosed in claim 2 may be within the literal scope of the genus of claim 1, it was never "named or otherwise exemplified" in the original patent

application. The Federal Circuit explained in a case similar to the facts present in the '117 patent by analogizing a genus and its constituent species to a forest and its trees. As the court explained:

> It is an old custom in the woods to mark trails by making blaze marks on the trees. It is no help in finding a trail . . . to be confronted simply by a large number of unmarked trees. Appellants are pointing to trees. We are looking for blaze marks which single out particular trees. We see none.

In re Ruschig, 379 F.2d 990, 994-95 (C.C.P.A. 1967).

As the Court further explained, "[s]pecific claims to single compounds require reasonably specific supporting disclosure and while we agree with the appellants, as the board did, that Naming [each species] is not essential, something more than the disclosure of a class of 1000, or 100, or even 48, compounds is required". Id at 994. See also *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571 (Fed. Cir. 1996) ("In the absence of such blazemarks, simply describing a large genus of compounds is not sufficient to satisfy the written description requirement as to particular species or sub-genuses."); *In re Wako Pure Chem. Indus., LTD.*, 4 Fed. Appx. 853, 857 (Fed. Cir. 2001) ("… just because a moiety is listed as one possible choice for one position does not mean that there is *ipsis verbis* support for every species or subgenus that chooses that moiety.").

In addition and as explained above, Applicants added approximately three columns of text from the '075 patent to the background section of the '117 patent application by amendment. However, this additional text cannot form the basis for the written description of claims 1-4 of the '117 patent for at least two reasons.

First, Applicants represented to the U.S. Patent & Trademark Office ("USPTO") during prosecution of the parent '736 application that the '075 patent did not render claims directed to the intermediate compounds as obvious. See 9/20/99 Amendment at p.6 discussed in the File

History section above.[14] Applicants cannot now assert that the very same reference they distinguished, the '075 patent, provides written descriptive support for the intermediate compounds recited in the process steps of claims 1-4. If the '075 patent discloses the intermediate compounds recited in claims 1-4, the claims are obvious as explained by the examiner during the prosecution history of the '736 application. If the '075 patent does not disclose the intermediate compounds, Applicants cannot rely on the '075 patent to support the written description of claims 1-4 in the '117 patent.

Second, Applicants distinguished the '075 patent as teaching inferior methods for making prostacyclin derivatives. By distinguishing the prior art to the '075 patent as inferior, a person skilled in the art would understand that the prior art does not form part of invention claimed in the '117 patent. See Col. 4:15-20. See *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1159 (Fed. Cir. 1998)(Finding that discussion in the specification of prior art which the application distinguished as inferior did not support claimed subject matter.).

V. THE ASSERTED CLAIMS OF U.S. PATENT NO 7,999,007 ARE INVALID AS ANTICIPATED UNDER 35 U.S.C. §102 AND OBVIOUS UNDER 35 U.S.C. § 103

A. Background Facts Leading up to Filing of the '007 Patent

In 1991, an Investigational New Drug Application was filed with the FDA seeking approval to market treprostinil for the treatment of pulmonary hypertension, and this IND was inactive from 1992 to 1997. March 9, 2001 Clinical Review by Drs. Karkowsky, Stockbridge, and Throckmorton at pp. 1-2 ("Clinical Review"). Then, United Therapeutics ("UTC") met with the FDA in 1998 and 1999 prior to filing its NDA seeking approval to market a subcutaneous

[14] Clearly the '075 patent disclosed treprostinil and pharmaceutically acceptable salts thereof as discussed under sections pertaining to the '222 patent. When Applicants distinguished the '075 patent, the claims were directed to the intermediate compounds, not the products produced by such compounds in the process as is now claimed in the '117 patent.

infusion of treprostinil for the treatment of pulmonary hypertension on October 16, 2000. *Id.* In support of its NDA, UTC provided data from two pivotal clinical trials designed to show efficacy over placebo. *See id.* at pp. 54, 163-168. However, while there was a trend of increased efficacy for treprostinil, UTC's results failed to meet the pre-specified efficacy benchmarks. *Id.* More concerning, though, was the near-universal incidence among patients taking treprostinil of severe pain at the site of infusion. *Id.* at pp. 27, 54, 163-168; March 14, 2002 Medical Officer Review by Dr. Karkowsky. In fact, in its NDA, UTC reported that during another clinical trial involving subcutaneous treprostinil, 91% of patients took some sort of analgesic to help with the pain, and 35% were prescribed opiates. Clinical Review at p. 27.

In light of these results, the FDA was hesitant to approve Remodulin. While acknowledging that there might be some clinical benefit, the reviewers were concerned by the high incidence of infusion site pain severe enough to warrant widespread treatment with narcotics. *See* December 8, 2000 Minutes of Meeting between UTC and FDA; January 25, 2001 Minutes of Meeting between UTC and FDA; Clinical Review, March 12, 2001 Minutes of Teleconference between UTC and FDA; April 11, 2001 Minutes of Meeting between UTC and FDA; June 8, 2001 Minutes of Teleconference between UTC and FDA; June 22, 2001 Minutes of Meeting between UTC and FDA. However, after numerous meetings between UTC personnel and the FDA reviewers, and a presentation to the FDA's Cardio-Renal Scientific Advisory Board, it was agreed that the NDA would be approved, contingent upon post-approval clinical trial data showing clinically meaningful efficacy. *See* November 15, 2001 Memo to Dr. Robert Temple; January 7, 2002 Minutes of Teleconference between UTC and FDA; February 8, 2002 Approval Letter.

However, even after Remodulin was approved, infusion site pain remained a problem. For example, contemporaneous articles note the high incidence of severe site infusion pain in patients administered subcutaneous Remodulin. McLaughlin, V. V., *et al.* "Efficacy and Safety of Treprostinil: An Epoprostenol Analog for Primary Pulmonary Hypertension," *Journal of Cardiovascular Pharmacology*, Vol. 41, pp. 293-99, at p. 296-98 (2003)("McLaughlin"); Simonneau, G., *et al.*, "Continuous Subcutaneous Infusion of Treprostinil, a Prostacyclin Analogue, in Patients with Pulmonary Arterial Hypertension," *American Journal of Respiratory Critical Care Medicine*, Vol. 165, pp. 800-04, at p. 802-04 (2002)("Simonneau"). UTC attempted to address this problem by filing a Supplemental NDA in January 2004 seeking approval to amend the Remodulin labeling to include an intravenous route of administration. *See* February 6, 2004 Letter from Zelda McDonald to Dean Bunce.

UTC's NDA for Remodulin was initially directed to administration of a treprostinil solution at a neutral pH administered via subcutaneous injection. The subcutaneous route of injection was initially chosen because it was thought to be preferable to the intravenous route used for Flolan for a variety of reasons. For example, while intravenous Flolan was known to be highly effective, the drug is unstable at neutral pH values and has a short half-life, so continuous intravenous infusion is necessary. *See generally,* McLaughlin, Simonneau; Barst, et al, "Long-term Outcome in Pulmonary Arterial Hypertension Patients Treated with Subcutaneous Treprostinil," *Eur. Respir. J.*, Vol. 28, No. 6, pp. 1195-1203 (2006). Potentially life-threatening complications from continuous intravenous administration include "catheter-related infections and temporary interruption of the infusion due to malfunction of the pump or dislodgment of the central venous catheter." *Id.* Treprostinil, unlike prostacyclin, is stable at room temperature and

at a neutral pH and has a longer half-life, so it can be more easily administered subcutaneously as well as intravenously. Simonneau at p. 800

Subcutaneous administration obviates the increased risk of infection and thrombosis associated with continuous intravenous administration. Simonneau at p. 800. However, utilizing a subcutaneous mode of administration necessarily impacts the choice of pH used for the formulation. It was well-known that subcutaneous delivery of a solution having a high pH would cause skin irritation and infusion site pain. *See generally* Berner, Bret, *et al.* "The Relationship Between pKa and Skin Irritation for a Series of Basic Penetrants in Man, *Fundamental and Applied Toxicology*, Vol. 15, pp. 760-766 (1990); Schmid-Wendtner, M.-H. & Korting, H.C., "The pH of the Skin Surface and Its Impact on the Barrier Function," *Skin Pharmacol. Physiol.* Vol. 19, pp. 296-302 (2006); Schmid-Wendtner, M.-H. & Korting, H.C., pH and Skin Care, Chapters 7-12 (2007); Tokumoto, S., *et al.*, "Effect of electroporation and pH on the iontophroetic transdermal delivery of human insulin," *International Journal of Pharmaceutics*, Vol. 326, pp. 13-19 (2006); EP 0347243. Accordingly, treprostinil was originally formulated in a solution having a neutral pH so that it would be appropriate for subcutaneous administration. When UTC submitted its supplemental NDA for intravenous administration, UTC maintained a neutral pH for its intravenous preparation.

At the time UTC submitted its supplemental NDA for intravenous administration, it had not yet completed the required post-marketing clinical trial showing efficacy of Remodulin. *See* July 6, 2004 Clinical Review by Dr. Karkowsky. UTC also did no additional clinical testing to support its sNDA for IV administration. *See id.* Instead, UTC submitted the results of non-clinical testing in dogs and rats, as well as a pharmacokinetics study done on healthy individuals comparing the bioavailability of treprostinil administered intravenously and subcutaneously after

72 hours. *Id.*; September 1, 2004 Pharmacology Review by Dr. Joseph; April 12, 2004 Clinical Pharmacology and Biopharmaceutics Review by Dr. Beasley. The FDA reviewers were concerned with the lack of clinical data, as further explained below. For example, in an April 9, 2004 letter to UTC, an FDA reviewer identified as a possible review issue that UTC provided "no data that define the safety of Remodulin when the drug is administered by way of a central intravenous line," and instead used safety information from the intravenous administration of Flolan in the proposed label. April 9, 2004 Letter from Doug Throckmorton to Dean Bunce.

The FDA Clinical Reviewer expressed concern at the notion of approving this new mode of administration without the benefit of any clinical testing, even that which was needed for approval of the original NDA. *See generally* July 6, 2004 Clinical Review by Dr. Karkowsky. The Clinical Reviewer noted the concerns of heighted risk associated with intravenous delivery and concluded that if approval was recommended, intravenous administration should be reserved for those patients that could not tolerate subcutaneous administration. *Id.*

In response to a September 15, 2004 information request from the FDA, UTC provided the case report forms for the ongoing investigator-initiated clinical study that was directed to evaluating the efficacy and safety of intravenous Remodulin. *See* September 15, 2004 Letter from Edward Fromm to Dean Bunce; October 25, 2004 Medical Officer Review by Dr. Karkowsky. As part of this submission, UTC provided case reports for thirty-eight patients who were administered intravenous Remodulin. October 25, 2004 Medical Officer Review by Dr. Karkowsky. Based on his review of UTC's data, the Medical Reviewer identified numerous adverse events (infection or pain) that were likely related to the intravenous route of infusion. *Id.*; Division of Cardio-Renal Drug Products, Divisional Memorandum, November 24, 2004. The FDA Medical Reviewer reaffirmed his original finding that if the sNDA was approved, only

those patients who could not tolerate subcutaneous Remodulin should receive intravenous Remodulin. *Id.* Ultimately the FDA approved this sNDA, subject to the same clinical study commitments accompanying approval of the original application. Division of Cardio-Renal Drug Products, Divisional Memorandum, November 24, 2004; November 24, 2004 Letter from Norman Stockbridge to Dean Bunce; November 29, 2004 Project Management Overview by Allis.

In the meantime, in early 2002, physicians began noticing an increased frequency of gram-negative infections in patients receiving IV Remodulin, relative to patients receiving IV Flolan. Eventually, these concerns were reported to the Centers for Disease Control and Prevention ("CDC"). This prompted the CDC to sponsor a study that confirmed the anecdotal reports and demonstrated that IV-administered Remodulin was associated with greater catheter-related bloodstream infections ("BSIs"), particularly with gram-negative bacteria, compared to IV Flolan. *See generally* CDC, "Bloodstream Infections Among Patients Treated with Intravenous Epoprostenol or Intravenous Treprostinil for Pulmonary Hypertension -- Seven Sites, United States 2003-2006," MMWR, Vol. 56, No. 8 pp. 170-72 (March, 2007); *see also* Kallen et al, "Bloodstream Infections in Patients Given Treatment with Intravenous Prostanoids," *Infections Control and Hospital Epidemiology*, Vol. 29, No. 4, pp. 342-49 (April 2008) (reporting results of a study conducted by the CDC and suggesting the higher pH value of Flolan as a potential cause of the lower infection rate compared to Treprostinil). The report of the CDC study states:

> This report describes the results of that investigation, which indicated that, based on combined data from seven separate PAH treatment centers, pooled mean rates of BSI (primarily gram-negative BSI) were significantly higher for patients on treprostinil than for those on epoprostenol. The results do not suggest intrinsic contamination of IV treprostinil as a cause of the infections; the difference in rates might have

> been caused by differences in preparation and storage of the two agents, differences in catheter care practices, or differences in the anti-inflammatory activity of the agents. Health-care providers who care for PAH patients should be aware of these findings. Further investigation is needed to determine the causes of the different infection rates at centers where this was observed and to determine whether such a difference exists in other PAH treatment centers.

The Report further explains:

> The investigation described in this report identified higher overall and gram-negative BSI rates among PAH patients receiving IV treprostinil compared with IV epoprostenol among patients treated in seven centers. Although the cause of this difference is unclear, the variety of organisms involved and the absence of bacterial growth in vials of used IV treprostinil obtained from patients with BSIs argue against intrinsic contamination of IV treprostinil or its diluents as a cause of the apparent BSI rate increase. At least three hypotheses exist that might explain the difference. First, differences in practices involved in the preparation and storage of the two agents might create different levels of risk for BSI.

Thus, the CDC hypothesized that one of the possible reasons for greater infection risk for IV Remodulin relative to IV Flolan was the difference in preparation of the two products. *Id*.

After the CDC Report was published, UTC needed to find a solution to this line infection problem. At this point, UTC, along with the rest of the public, had several key pieces of information to guide its search for a solution. First, as discussed below, it was well-known that Flolan resulted in a lower incidence of central line infections when compared to other intravenous preparations generally, as well as when compared to Remodulin specifically. Second, it was known that Flolan was reconstituted in a buffer having a high pH prior to administration, while Remodulin was reconstituted in a solution having a neutral pH prior to administration. Third, as discussed in detail below, it was well known that solutions having a high pH prevented bacterial growth. To summarize, the only difference between Flolan and Remodulin was the solution used to reconstitute the drug, and the higher pH of the Flolan diluent was a characteristic known to prevent bacterial growth. Accordingly, UTC adopted this

exceedingly obvious solution to its central line infection problem and began reconstituting Remodulin with the Flolan buffer prior to administration. UTC filed an additional supplemental NDA in 2007 seeking to amend its label to state that Remodulin could be reconstituted with the Flolan diluent prior to administration. UTC also filed the provisional application to which the '007 patent claims priority in September 2007.

B. Prosecution History of the '007 Patent.

The '007 patent, entitled "Buffer Solutions Having Selected Bactericidal Activity Against Gram-Negative Bacteria and Methods of Using Same," issued on August 16, 2011 and claims a priority date of September 7, 2007. The '007 patent was allowed from U.S. Application No. 12/276,707 ("the '707 application"), filed November 24, 2008, which claims to be a continuation of U.S. Application No. 12/205,200, which in-turn claims priority to provisional Application No. 60/976,017, filed September 7, 2007.

There are 26 claims, with claims 1, 11 and 22 being independent. UTC is asserting claims 1-5, 7-17 and 19-26 ("asserted claims"). The asserted claims read as follows:

> **1**. A method of selectively killing gram negative bacteria and inhibiting the growth of gram positive bacteria in a pharmaceutical preparation comprising an active agent selected from the group consisting of treprostinil and treprostinil sodium, the method comprising supplying the active agent with a buffer comprising glycine and having a pH of greater than 10 with low buffer capacity.
>
> **2**. The method of claim **1**, wherein the active agent is treprostinil sodium.
>
> **3**. The method of claim **1**, wherein the buffer further comprises sodium hydroxide.
>
> **4**. The method of claim **1**, wherein the buffer has a pH between about 10 to about 12 with low buffer capacity.
>
> **5**. The method of claim **4**, wherein the buffer has a pH

7. The method of claim **1**, wherein the active agent is supplied at a concentration between about 0.001 mg/mL to about 1 mg/mL.

8. The method of claim **2**, wherein the treprostinil sodium is supplied at a concentration between about 0.004 mg/mL to about 0.13 mg/mL.

9. The method of claim **1** further comprising injecting the pharmaceutical preparation into a mammal in need thereof.

10. The method of claim **4**, wherein the pharmaceutical preparation is injected intravenously into a mammal in need thereof.

11. A method of reducing the occurrence of blood stream infections in a mammal being treated with an active agent comprising administering to the mammal the active agent with a buffer comprising glycine and having a pH of greater than 10, wherein the active agent is selected from the group consisting of treprostinil and treprostinil sodium, and wherein the administration reduces the gram negative bacteria and inhibits the growth of gram positive bacteria.

12. The method of claim **11**, wherein the human subject has pulmonary arterial hypertension.

13. The method of claim **11**, where in the active agent is administered intravenously.

14. The method of claim **11**, wherein the active agent is treprostinil sodium.

15. The method of claim **11**, wherein the buffer further comprises sodium hydroxide and has a pH between about 10.2 to about 10.8.

16. The method of claim **11**, wherein the buffer has a pH between about 10 to about 12 with low buffer capacity.

17. The method of claim **16**, wherein the buffer has a pH

19. The method of claim **11**, wherein the active agent is supplied at a concentration between about 0.004 mg/mL to about 0.13 mg/ml.

20. The method of claim **14**, wherein the treprostinil sodium is supplied at a concentration between about 0.004 mg/mL to about 0.13 mg/mL.

21. The method of claim **1** wherein the administering is injecting the pharmaceutical preparation into a mammal in need thereof.

22. A pharmaceutical composition comprising an active agent selected from the group consisting of treprostinil and treprostinil sodium in a solution comprising glycine and having a pH greater than 10.

23. The composition of claim **22**, wherein the solution further comprises sodium hydroxide.

24. The composition of claim **22**, wherein the solution has a pH between about 10 to about 12.

25. The composition of claim **24**, wherein the solution has a pH between about 10.2 to about 10.8.

26. The composition of claim **22**, wherein the active agent is treprostinil sodium.

The original claims of the '707 application[15] were directed to a solution in which "epoprostenol sodium is not the sole active agent" or in which "the active agent is not epoprostenol sodium." In a first office action, the claims were rejected as obvious over the combination of Gomberg-Maitland et al., *Am. J. Respir. Crit. Care Med.*, vol. 172, pp. 1586-1589 (2005), which teaches the use of intravenous treprostinil to treat patients with pulmonary hypertension; McLaughlin et al., *New England Journal of Medicine*, vol. 338, pp. 273-77 (1998), which teaches the use of intravenous epoprostenol to treat pulmonary hypertension; and the prescribing information for FLOLAN® from GlaxoSmithKline, which teaches epoprostenol in a glycine buffer with a pH between 10.2 and 10.8. The claims were also rejected as indefinite under 35 U.S.C. § 112, ¶ 2 for claiming a solution with a buffer "having a pH of greater than about 10" and "having a pH of less than about 4.5."

In response to the obviousness rejection, the patentees removed the references to epoprostenol from the claims, specifically claimed treprostinil and treprostinil sodium as the active agents, and argued that "the skilled artisan would have had no reason or incentive to select the diluent used in FLOLAN from among the myriad of heretofore equivalent alternatives proffered by the prior art (e.g., sterile water, bacteriostatic water, normal saline (0.9%), bacteriostatic normal saline, 5% dextrose in water, etc.)." In response to the indefiniteness rejection, the patentees amended the independent claims to require that, rather than the buffer having a pH greater than "about 10," the pH must be "greater than 10" or "less than 4.5." A further amendment to claim 1 prior to allowance removed the language that claimed solutions with a pH less than 4.5. The claims were then allowed, with the examiner noting that a new reference, Phares et al., *Am. J. Health-Sys. Pharm.*, vol. 60, pp. 916-922 (2003), was the closest

[15] The parent application to the '200 application was expressly abandoned before the first office action.

art of record. The patentees then amended the claims after allowance, which they contended was necessary "to correct errors of omission in the Examiner's Amendment which accompanied the Notice of Allowance".

C. EP Patent Application Publication No. 0347243 A1 ("EP '243 publication) Anticipates the Asserted Claims of the '007 Patent

The EP '243 publication was published December 20, 1989 and is entitled "Prostaglandin Analogues for Use in Medicine." The EP '243 publication explicitly discloses treprostinil and also discloses its salts. EP '243 publication at 4:1-15, 47-63. The EP '234 publication further discloses that the active compound or physiologically acceptable salts thereof can be formed as infusion fluids having from 10 ng to 10 μg per milliliter. *Id*. at 4:64-5:6. The EP '243 publication states that formulations suitable for parenteral administration include sterile aqueous formulations of treprostinil or a salt thereof, mixed with a glycine buffer and containing between 0.1 to 5% w/v of the active compound. *Id.* at 5:48-55. Example 1 describes the use of a series of glycine buffer solutions having a pH of 10.5 that were prepared with varying amounts of treprostinil. *Id.* at 6:6-33. The solutions were successively administered intravenously to a cat in an experimental hypertension model. *Id.* The results of this experiment indicated that treprostinil administered intravenously in a glycine buffer having a pH of 10.5 could reduce pulmonary vasoconstriction and blood pressure. *Id.* Accordingly, the EP '243 publication teaches a person of ordinary skill in the art to administer treprostinil in a glycine buffer having a pH of 10.5, and that this composition can be administered intravenously to treat pulmonary hypertension.[16] *Id.*

[16] Similar disclosure can be found in Australian Patent No. 623147, published December 21, 1989, Canadian Patent No. 1,327,524, issued March 8, 1994, and Portuguese Patent Publication No. PT90888, published December 29, 1989. The '243 publication is a related application of the '222 patent, which discloses administering treprostinil in a glycine buffer.

(continued…)

The asserted composition claims of the '007 patent are directed to compositions containing treprostinil or its sodium salt in a solution comprising glycine and having a pH of greater than 10. Because the EP '243 publication discloses a composition including treprostinil and its sodium salt in a glycine buffer having a pH greater than 10, the EP '243 application anticipates composition claims 22-26 of the '007 patent. Furthermore, while independent claims 1 and 11 (and claims dependent thereon) recite the use of such compositions to kill or reduce gram negative bacteria and inhibit the growth of gram positive bacteria, the solution administered in Example 1 in the EP '243 publication would inherently have these same properties.

Administration of treprostinil in a glycine buffer with a pH of 10.5 as taught in the EP '243 publication would necessarily result in killing and/or inhibiting the growth of bacteria. It was well-known that solutions having an alkaline pH, for example greater than 10, kill and/or inhibit the growth of bacteria. Brannan, Cosmetic Microbiology – A Practical Handbook, pp. 47-48 (CRC Press 1997); *see also* Catalano, et al, "Incidence of Salmonella in Pennsylvania Egg Processing Plants and Destruction by High pH," *J. Food Prot.*, Vol. 57, pp. 587-591 (1994); Kinner, et al, "Effect of Temperature, pH and Detergent on the Survival of Bacteria Associated with Shell Eggs," *Poult. Sci.*, Vol. 60, pp. 761-767 (1981); Laird, et al, "Survival of Listeria Monocytogenes in Egg Washwater," *Int. J. Food Microbiol*, Vol. 12, pp. 115-122 (1991); Mendonca, et al, "Destruction of Gram-Negative Food-Borne Pathogens by High pH Involves Disruption of the Cytoplasmic Membrane," *Applied and Environmental Microbiology*, Vol. 60, No. 11, p. 4009-4014 (1994); Pearson, et al, "Survival and Transport of Bacteria in Egg Washwater," "*Appl. Environ. Microbiol.*," Vol. 53, pp. 2060-2065 (1987); Southam, et al,

"Survival and Growth of Yersinia Enterocolitica in Egg Washwater," *J. Food Prot*., Vol. 50, pp. 103-107 (1987); Lynch et al, "Bacterial Counts in Canine Duodenal Fluid After Exposure to Saline, Sodium Bicarbinate and Hypertonic Dextrose Solutions Used to Maintain Patency of Chronically Implanted Catheters," *Laboratory Animals*, Vo. 33, pp. 143-48 (1999).

Moreover, in particular, it was known that when prostacyclin is reconstituted in an alkaline buffer having a pH greater than 11, the composition "is highly resistant to microorganism [sic] and can pass USP preservative effectiveness test." WO2007/092343, at p. 7, ll. 4-22; U.S. Patent Publication No. 2009/0088468, at paragraphs 17, 20. The alkaline buffer was identified as responsible for causing the antimicrobial activity of the composition. *Id.* Thus, the EP '243 publication anticipates claims 1-5, 7-17, and 19-26 of the '007 patent.[17]

Further, a person of ordinary skill in the art at the time of the invention would understand that a glycine buffer having a pH of 10.5 used in a pharmaceutical preparation would necessarily have a low buffer capacity. *See, e.g.,* Remington, pp. 246-46, 804; *see also* Li, P. & Zhao, Luwei, "Developing early formulations: Practice and perspective," *International Journal of Pharmaceutics*, Vol. 341, pp. 1-10 (2007) ; U.S. Patent No. 4,088,759 to Woog (1978); WO '343 publication. In particular, it was known that pharmaceutical preparations designed for intravenous administration having a high pH would necessarily have a low buffering capacity to ensure that the pH of the blood remains constant during infusion. *Id.*

D. It Would Have Been Obvious to Use a Glycine Buffer with a pH greater than 10 to Selectively Kill Gram-Negative Bacteria and Inhibit the Grown of Gram-Positive Bacteria.

The discussion of the use of prostacyclin and prostacyclin analogues such as treprostinil to treat pulmonary hypertension in connection with the '222 patent provides contextual

[17] The EP '243 publication was not cited during prosecution of the '007 patent.

background and is partially relevant here. Accordingly, that discussion is incorporated herein by reference.

It was well known at the time of the invention that prostacyclin (also known as epoprostenol) suffers greater instability in environments with pH lower than 10. Barst, et al. "A Comparison of Continuous Intravenous Epoprostenol (Prostacyclin) With Conventional Therapy for Primary Pulmonary Hypertension," *New England J. of Med*., Vol. 334, No. 5, pp. 296-301 (Feb. 1996); Eells, "Advances in Prostacyclin Therapy for Pulmonary Arterial Hypertension," *Clinical Care Nurse*, Vol. 24, No. 2, pp. 42-54 (2004); U.S. Patent 4,335,139. Thus, the commercially available intravenous prostacyclin product sold for many years before the critical date under the brand name Flolan includes a diluent that comprises a glycine buffer and has a pH of greater than 10. *See* Flolan Package Insert.

Treprostinil has the advantage that it is stable in pH neutral environments. Barst, et al, "Long-term Outcome in Pulmonary Arterial Hypertension Patients Treated with Subcutaneous Treprostinil," *Eur. Respir. J.*, Vol. 28, No. 6, pp. 1195-1203 (2006). As explained above, UTC first sought approval for a subcutaneous mode of administration, and subcutaneous administration required a neutral pH to minimize site pain. Additionally, line infections are not a concern with subcutaneous administration, because the subcutaneous route itself provides a barrier to prevent infection. Accordingly, UTC's approved treprostinil intravenous/subcutaneous product, marketed under the brand name Remodulin, initially was sold with a diluent having a pH in the range of 6 to 7 and did not include glycine. Remodulin Package Insert (2006). Flolan and Remodulin intravenous products have competed since Remodulin was approved in 2002.

As explained above, the CDC issued a report in 2006 describing an increased incidence of central line infections resulting from intravenous administration of Remodulin when

compared to intravenous administration of Flolan. The CDC's cautionary warning and greater risk of infection for Remodulin, together with its hypothesis that a potential cause of the infection risk could reside in the differences in how the two products are prepared would have inspired skilled artisans at the time of the '007 patented invention to compare and contrast the preparation differences between Remodulin and Flolan. The skilled artisan would have learned that, whereas Flolan is sold with a diluent having a glycine buffer with a pH greater than 10, the preparation of Remodulin did not involve glycine and the pH was considerably lower, *i.e.*, 6-7. Flolan Product Insert (1999); Remodulin Package Insert (2006).

One skilled in the art at the time of the '007 patent invention would have understood that subcutaneous and intravenous treatments, especially those using catheter technology, were prone to causing microbial infection, including infections caused by gram-negative and gram-positive bacteria. *See, e.g.*, FDA, Guide for Industry: Catheter-Related Bloodstream Infections – Developing Antimicrobial Drugs for Treatment, pp. 1-17 (1999); O'Grady et al, "Guidelines for the Prevention of Intervascular Catheter-Related Infections," *Pediatrics*, Vol. 110, No. 5 (Nov. 2002); Akagi et al, "Prevention of Catheter-Related Infections Using A Closed Hub System in Patients with Pulmonary Hypertension," *Circulation J.*, Vol. 71 pp. 559-64 (April 2007); Salzman et al, "Relevance of the Catheter Hub as a Portal for Microorganisms Causing Catheter-Related Bloodstream Infections," *Nutrition*, Vol. 13, No. 4 (suppl.), pp. 15S-17S (1997).

The skilled artisan also would have known that products or environments with pH higher than 10 ordinarily inhibits growth of or kills microorganisms, including gram-negative and gram-positive bacteria. Kabara, *Preservative-Free and Self-Preserving Cosmetics and Drugs, Principles and Practice*, Chapters 1, 2 and 11 (Marcel Dekker, Inc. 1997)("Kabara"); Brannan, Cosmetic Microbiology – A Practical Handbook, pp. 47-48 (CRC Press 1997); *see also* Denyer

et al, Guide to Microbiological Control in Pharmaceuticals and Medical Devices, 2d Ed., pp. 24-50 (CRC Press 2006); Catalano, et al, "Incidence of Salmonella in Pennsylvania Egg Processing Plants and Destruction by High pH," *J. Food Prot.*, Vol. 57, pp. 587-591 (1994); Kinner, et al, "Effect of Temperature, pH and Detergent on the Survival of Bacteria Associated with Shell Eggs," *Poult. Sci.*, Vol. 60, pp. 761-767 (1981); Laird, et al, "Survival of Listeria Monocytogenes in Egg Washwater," *Int. J. Food Microbiol*, Vol. 12, pp. 115-122 (1991); Mendonca, et al, "Destruction of Gram-Negative Food-Borne Pathogens by High pH Involves Disruption of the Cytoplasmic Membrane," *Applied and Environmental Microbiology*, Vol. 60, No. 11, p. 4009-4014 (1994); Pearson, et al, "Survival and Transport of Bacteria in Egg Washwater," "*Appl. Environ. Microbiol.*," Vol. 53, pp. 2060-2065 (1987); Southam, et al, "Survival and Growth of Yersinia Enterocolitica in Egg Washwater," *J. Food Prot.*, Vol. 50, pp. 103-107 (1987); Hugo, W.B. *Pharmaceutical Microbiology* (Wiley & Sons 1998). For example, Kabara teaches that "[s]ome products use alkaline pH as part of their preservative system." Kabara at p. 17. Kabara further states as follows:

> The ability of microorganisms to grow/survive also becomes increasingly difficult as the pH increases above the neutrality range. Products with pH values greater than pH 9 often require little or no chemical preservatives, whereas similar formulas in the neutral pH range required added preservatives to be adequately preserved….As with the high-acid products, the highly alkaline products are much easier to preserve than are similar products with pH values in the neutral range.

Kabara at p. 246.

The U.S. Pharmacopeia further confirms that it was common knowledge in the pharmaceutical industry that a high pH inhibits bacterial growth. For example, U.S.P. 32 <1112>, which deals with "water activity" of pharmaceutical compositions and its impact on inhibiting bacterial growth, states that other product attributes, such as "high pH," help to

prevent microbial growth. With respect to catheter-related infections, it was known that fluids with elevated pH cause inhibition of bacterial growth. Lynch et al, "Bacterial Counts in Canine Duodenal Fluid After Exposure to Saline, Sodium Bicarbinate and Hypertonic Dextrose Solutions Used to Maintain Patency of Chronically Implanted Catheters," *Laboratory Animals*, Vo. 33, pp. 143-48 (1999). In fact, it was known as early as 2004 that, based on testing, patients treated with intravenous epoprostenol (Flolan), which was known to have a glycine buffer and a pH of greater than 10, experienced a dramatically lower incidence of bacterial infection than patients treated with other intravenous catheter-delivered medications.[18] Oudiz, "Micrococcus-Associated Central Venous Catheter Infection in Patients with Pulmonary Arterial Hypertension," *Chest*, Vol. 126, No. 1, pp. 90-94 (July 2004).

Moreover, it was known that when prostacyclin is reconstituted in an alkaline buffer having a pH greater than 11, the composition "is highly resistant to microorganism [sic] and can pass USP preservative effectiveness test." WO2007/092343, at p. 7, ll. 4-22; U.S. Patent Publication No. 2009/0088468, at paragraphs 17, 20. In this composition, the alkaline buffer was identified as responsible for causing the antimicrobial activity of the composition. ***Id.***

It would thus have been natural at the time of the claimed invention for the skilled artisan to combine the disclosures of the 2007 CDC report, the differences in the Flolan and Remodulin preparations as set forth in their respective packet inserts and the disclosures of the Cosmetic Microbiology reference (or any one or more of the Denyer, Catalano, Kinner, Laird, Mendonca,

[18] Flolan is a "preservative-free" formulation in that it does not include an additive antimicrobial agent. In 1995, when Flolan was approved, the FDA required (and still requires) that compositions formulated for injection include "[a] suitable substance of mixture of substances to prevent the growth of microorganisms…unless the active ingredients are themselves antimicrobial." USP 23, <1> Injections at p. 1651. An applicant satisfies this requirement by showing that the formulation passed the required antimicrobial effectiveness testing. *Id.* Flolan does not include an antimicrobial substance in its reconstituted vehicle. Flolan Product Insert (1999). Thus, it was known that Flolan administration resulted in fewer infections than other intravenous preparations, and that Flolan did not include an antimicrobial agent other than the alkaline buffer.

Southam, WO2007/092343 or U.S. Patent Publication No. 2009/0088468) to arrive at the use of an alternative diluent for Remodulin having a glycine buffer with a pH of 10 to resolve the problems of increased risk of bloodstream infections warned about by the CDC. The '222 patent previously disclosed that treprostinil and its salts could be provided intravenously and could be mixed with a glycine buffer and Oudiz disclosed that the Intravenous Flolan product was known to cause far less infections that other catheter-infused medications. The EP '243 publication taught to use treprostinil or its salts with a glycine buffer having a pH of 10.5 in intravenous treatments.

Furthermore, a person of ordinary skill in the art at the time of the invention would understand that a glycine buffer having a pH of 10.5 used in a pharmaceutical preparation would necessarily have a low buffer capacity. *See, e.g.,* Remington, pp. 246-46, 804; *see also* Li, P. & Zhao, Luwei, "Developing early formulations: Practice and perspective," *International Journal of Pharmaceutics*, Vol. 341, pp. 1-10 (2007) ; U.S. Patent No. 4,088,759 to Woog (1978); WO '343 publication. In particular, it was known that pharmaceutical preparations designed for intravenous administration having a high pH would necessarily have a low buffering capacity to ensure that the pH of the blood remains constant during infusion. *Id.* Thus, it would have been obvious for a person of ordinary skill in the art formulating a glycine buffer having a pH greater than 10 for use in a pharmaceutical preparation to use a glycine buffer with a low buffering capacity.

The literature preceding filing of the '007 patent along with contemporaneous FDA documentation clearly shows that UTC was forced to address a serious problem with their IV Remodulin product. UTC knew that IV Remodulin resulted in an increased incidence of central line infections compared to Flolan, which was administered in a buffer having a high pH. UTC

adopted the obvious solution to its problem, which was to use the Flolan diluent with Remodulin. Thus, the asserted claims of the '007 patent are invalid as obvious under 35 U.S.C. § 103.

E. Secondary Considerations Do Not Mitigate or Negate the Obviousness of the Invention Claimed in the '007 Patent

UTC bears the burden of providing evidence of objective indicia of non-obviousness. *In re Huang*, 100 F.3d 135, 139 (Fed. Cir. 1996) "Evidence of secondary considerations does not always overcome a strong *prima facie* showing of obviousness." *Asyst Technologies, Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008); *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010); *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 417 (2007)).

Sandoz is unaware of any secondary considerations that negate the obviousness of the inventions of the asserted claims of the '007 patent. It is impossible for Sandoz to anticipate what secondary considerations UTC may rely upon in rebutting Sandoz's obviousness defenses. To the extent that UTC intends to rely on any secondary considerations, much of the evidence concerning such secondary considerations is likely to be in the possession of UTC, and not Sandoz, and UTC has not yet produced any such evidence. Consequently, Sandoz reserves the right to amend its invalidity contentions to address the evidence of alleged secondary considerations that UTC may hereafter produce. Sandoz will also address secondary considerations in its expert disclosures once it has the opportunity to assess UTC's secondary considerations, to the extent it relies on any, and supporting evidence.

1. Long-Felt Need and Failed Attempts by Others

There was no long-felt but unresolved need at the time of the invention for an appropriate high pH glycine buffer diluent for treprostinil effective in killing gram-negative bacteria and inhibiting the growth of gram positive bacteria. As discussed in Section V(A) above, the Flolan diluent (containing glycine and sodium hydroxide and having a pH of greater than 10) was

known and commercially available at least by 1995. As discussed in Section V(C), EP Patent Application Publication No. 0347243 A1 disclosed an intravenous treatment for pulmonary hypertension that contained treprostinil and glycine and had a pH of 10.5. As discussed in Section V(D), the CDC announced the problem of the higher incidence of catheter line infections for Remodulin compared to Flolan in 2007. Thus, there is no evidence of a long-felt need or failed attempts by others in this case.

2. Unexpected Results

To prove unexpected results, the patentee must first show what was expected. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007). Then, the patentee must show that the results obtained with the claimed invention, even if superior than what was taught in the prior art, were truly surprising. *Id.* The patentee must show that the results obtained were unexpected as compared with the closest prior art compound. *Pfizer*, 480 F.3d at 1370 (citing *Kao Corp. v. Unilever U. S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006)). In particular, the patentee must show that the claimed invention exhibits unexpected results over the prior art reference supporting the *prima facie* evidence of obviousness. *Aventis Pharma Deutschland GMBH v. Lupin, Ltd.*, 499 F.3d 1293, 1302 (Fed. Cir. 2007).

A showing of unexpected results requires that the results obtained differ "in kind and not merely in degree" when compared with the results obtained with the closest prior art reference. *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004)(quoting *In re Huang*, 100 F.3d 135, 139 (Fed. Cir. 1996)). Thus, the patentee must "produce evidence demonstrating 'substantially improved' results that are unexpected in light of the prior art." *Santarus, Inc. v. Par Pharm., Inc.*, 720 F. Supp. 2d 427, 457 (D. Del. 2010)(quoting *In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995)). Then, any such evidence must be "weighed against contrary

evidence indicating that the results were not unexpected or not a substantial improvement over the prior art." *Id.*

As discussed above in Section V(D) above, high pH solutions were known to kill or inhibit the growth of bacteria long before the critical date. (That section is incorporated herein by reference). Based on the CDC publication, it was also known by 2006 that the Flolan, which had a diluent containing a glycine buffer and sodium hydroxide with a pH greater than 10, was far less prone to cause bacterial infections than Remodulin which had a neutral pH diluent. Consequently, one of ordinary skill in the art would have expected a diluent with a pH greater than 10 and having a glycine buffer (and sodium hydroxide) together with treprostinil or its salts to be effective for killing gram-negative bacteria and inhibiting gram-positive bacteria in an intravenous treatment using catheters. The claimed result would have been expected.

3. Commercial Success

UTC has not produced evidence that its Remodulin product embodies the properties claimed in the '007 claims. UTC also has not yet produced any information reflecting sales of Remodulin, market share analysis, or other information from which to assess commercial success. It is Sandoz's belief that prescriptions and unit sales of Flolan and other third-party competitive products outstrip sales of Remodulin as a treatment for pulmonary hypertension. Other competitive products include Iloprost (a prostacyclin analog that is inhaled), Tyvaso (a treprostinil product that is inhaled) and Veletri (an intravenous prostacyclin administered in a buffer having a pH greater than 11). Commercial success cannot be shown where sales of a commercial embodiment of a patent remain low compared to competing products, sales growth has stagnated, and sales fell short of the patentee's expectations. *Santarus, Inc. v. Par Pharm., Inc.*, 720 F. Supp. 2d 427, 453-54 (D. Del. 2010). Moreover, commercial success is not probative if it is merely the result of marketing efforts and promotional offers. *See Brown &*

Williamson Tobacco Corp. v. Philip Morris Inc., 229 F.3d 1120, 1130 (Fed. Cir. 2000); *McNeil-PPC, Inc. v. L. Perrigo Co.*, 337 F.3d 1362, 1370 (Fed. Cir. 2003). UTC has not yet produced documents showing its advertising or promotional efforts.

Without the benefit of discovery, Sandoz reasonably believes that the reduced effectiveness of treprostinil compared to prostacyclin (Flolan), the relative failure of Remodulin as a subcutaneous treatment due to pain response by patients, and the higher risk of infection vis-à-vis Flolan has limited and adversely impacted the success of Remodulin in the marketplace.

There is also no link between any sales success of Remodulin and the claimed features set forth in the '007 patent. Commercial success is probative of non-obviousness "only if here is proof that the sales were a direct result of the unique characteristics of the claimed invention—as opposed to other economic and commercial factors unrelated to the quality of the patented subject matter." *In re Huang*, 100 F.3d at 140. Further, the commercial success must be "attributable to something disclosed in the patent that was not readily available in the prior art." *J.T. Eaton & Co., Inc. v. Atlantic Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997). Thus, commercial success is not probative of non-obviousness if the success "was due to unclaimed or non-novel features of the [claimed invention]". *Ormco Corp. v. Align Technology, Inc.*, 463 F.3d 1299k, 1312 (Fed. Cir. 2006). Moreover, commercial success must be due to "the subject matter that [the patentee] contends is nonobvious." *Friskit, Inc. v. Realnetworks, Inc.*, 306 F.3d Appx. 610, 617 (Fed. Cir. 2009). Here, there is no evidence that any purported commercial success achieved by Remodulin was due to the novel features of the claimed invention.

4. Acclaim and Acknowledgement of Success

Sandoz is unaware that Remodulin has been subject to any measure of acclaim. In fact, Remodulin garnered negative press in 2006-2008 because of reports of higher incidence of infection compared to Flolan. See Section V(A).

5. Copying

Copying is not a secondary consideration germane to ANDA litigation. "[A] showing of copying is not compelling evidence of non-obviousness in Hatch-Waxman cases due to the nature of the ANDA process." *Santarus, Inc. v. Par Pharm., Inc.*, 720 F.Supp.2d 427, 458 (D. Del. 2010); *see also Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, 642 F.Supp.2d 329, 373-74 (D. Del. 2009). "[T]he ANDA procedures established by the Hatch-Waxman Act require generic drug manufacturers to copy the approved drug. Variations undermine the FDA's ability to assume that if the patented drug is safe and effective, the generic competitor will also be safe and effective." *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, No. IP 99-38-C H/K, 2001 WL 1397403, at * 14 (S.D. Ind., Oct. 29, 2001). Thus, any evidence of copying is entitled to no probative value, and in any case, cannot overcome Sandoz's strong showing of obviousness.

6. Teaching Away

Teaching away requires an affirmative criticism or disparagement of the claimed invention, and a mere statement that a certain embodiment is preferred or optimal is insufficient. "A reference does not teach away, however, if it merely expresses a general preference of an alternative invention but does not criticize, discredit, or otherwise discourage investigation into the invention claimed." *Depuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009); *see also In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004); *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005). In considering whether a prior art reference teaches away, "all disclosures of the prior art, including unpreferred

embodiments, must be considered." *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989). Sandoz is unaware of any prior art reference that teaches away from using a treprostinil intravenous product having a glycine buffer with a pH greater than 10 to kill or inhibit the growth of bacteria. Any such reference, if it exists, must be read in light of the prior art identified and discussed in sections V(A), (C) and (D), all of which would have encouraged the skilled artisan at the time of the invention to use a high pH glycine buffer to reduce the risk of bacterial line infections.

VI. THE '007 PATENT CLAIMS ARE INVALID UNDER 35 U.S.C. § 112

A. Claims 1, 3-7, 9-10, 11-13, 15-19, 21 and 22-25 Are Invalid As Not Enabled Under 35 U.S.C. § 112(1).

The specification of the '007 patent does not provide a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains. In particular, the specification also does not enable a person skilled in the art to make and use the full scope of the claims 1, 3-7, 9-10, 11-13, 15-19, 21 and 22-25. Claims 1, 3-7, 9-10, 11-13, 15-19, 21 and 22-25 all require supplying or administering or composition of "treprostinil" or "treprostinil sodium" "with a buffer comprising glycine and having a pH of greater than 10" or "in a solution comprising glycine and having a pH greater than 10". Treprostinil, however, is a free acid. Treprostinil would be immediately converted to its salt form when supplied, administered, or in a solution having a pH greater than 10. The specification does not teach a person skilled in the art how to supply, administer, make, or use the free acid form of treprostinil in a solution having a pH of greater than 10 without undue experimentation. Accordingly, claim 1, 3-7, 9-10, 11-13, 15-19, 21 and 22-25 are not enabled.

B. Claims 4, 9, 10, 12, 16, 19, 20 and 21 Are Invalid Under 35 U.S.C. § 112(2).

The specification of the '007 patent fails to conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention. In particular, claims 4, 9, 10, 12, 16, 19, 20 and 21 are indefinite.

Claims 4 and 16 are indefinite for using terms that are inconsistent with the claims from which they depend. Claim 4 depends from claim 1 and claim 16 depends from claim 11. Both claims 4 and 16 contain the limitation "wherein the buffer has a pH between *about 10* to about 12 with low buffer capacity". Claims 1 and 11, in turn, read in pertinent part "with a buffer . . . having a pH of *greater than 10* with low buffering capacity". Pursuant to 35 U.S.C. § 112(4), "[a] claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers". Thus, claims 4 and 16 must be construed to recite that the buffer has both "a pH of greater than 10" and "between about 10 to about 12". However, the combination of limitations that require the buffer to be both "greater than 10" and "between about 10 . . ." renders the claims indefinite. As explained by the Examiner in the Office Action dated 6/17/2010 at p. 3:

> Either the limitation is "greater than" or the limitation is "about." Greater than is a static point while about is a dynamic point. As a result the recitation of "greater than about"-renders the claims vague and indefinite. A point cannot be simultaneously static and dynamic.

Claims 9, 10 and 21 are indefinite because their scope cannot be determined. Each of these claims calls for injecting the pharmaceutical preparation recited, directly or indirectly, from claim 1 "into a mammal in need thereof". However, claim 1 does not describe any underlying condition for any mammal. Rather, claim 1 is directed to a "method of selectively killing gram negative bacteria and inhibiting the growth of gram positive bacteria in a pharmaceutical preparation". Claim 1 is not directed to treating a mammal with any particular condition and

none are implicated. Therefore, a person skilled in the art would not know what "need" the mammal has for receiving an injection of the pharmaceutical preparation and thus claims 9, 10 and 21 are indefinite.

Claims 12, 19, 20 and 21 are indefinite for using terms that have no antecedent basis and thus the scope of the claims cannot be determined. For example, claim 12 recites "the human subject"; claims 19 and 20 recite "is supplied", and claim 21 recites "the administering". Claims 12, 19 and 20 all depend from claim 11. But claim 11 does not describe a human subject or supplying the active agent. Claim 21 relates back to claim 1 but there is no administration step. Hence, a person skilled in the art would not be able to ascertain the scope of claims 12, 19, 20 and 21 and they are thus indefinite.

C. Claims 4 and 16 Are Invalid Under 35 U.S.C. § 112(4).

Claims 4 and 16 of the '007 patent are invalid under 35 U.S.C. § 112(4). Pursuant to 35 U.S.C. § 112(4), "a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed" and "incorporate by reference all of the limitations of the claim to which it refers". Dependent claims which fail to comply 35 U.S.C. § 112(4) are invalid. See *Pfizer Inc. v. Ranbaxy Lab. Ltd.*, 457 F.3d 1284 (Fed. Cir. 2006) *citing* 35 U.S.C. § 282(3) ("[i]nvalidity of the patent or any claim in suit for failure to comply with *any* requirement of sections 112 or 251 of this title is expressly included among the available defenses to an infringement suit.")(emphasis original).

Claim 4 depends from claim 1 and claim 16 depends from claim 11. Both claims 4 and 16 contain the limitation "wherein the buffer has a pH between about 10 to about 12 with low buffer capacity". Claims 1 and 11, in turn, read in pertinent part "with a buffer . . . having a pH of greater than 10 with low buffering capacity" Since claims 4 and 16 require the buffer only "has a pH between *about 10* to about 12" rather than having "a pH of *greater than 10*", the

claims do not "incorporate by reference all of the limitations of the claim to which it refers" and "then specify a further limitation of the subject matter from which they depend". In other words, claims 4 and 16 do not narrow the scope of claims 1 and 11, respectively. Instead, the claims contain overlapping subject matter. The Federal Circuit has held that a dependent claim that violates 35 U.S.C. § 112(4) in this manner is invalid. See *Pfizer Inc. v. Ranbaxy Lab. Ltd.*, 457 F.3d 1284 (Fed. Cir. 2006).

VII. DISCLOSURES PURSUANT TO LOCAL PATENT RULE 3.4(D)

Pursuant to Local Patent Rule 3.4(d), Sandoz further produces herewith a CD containing documents Bates numbered SANDOZ-TREP as follows:

(a) A copy of the prior art identified in Sandoz's Invalidity Disclosures which does not appear in the file history of the '222, '117, or '007 patents: SANDOZ-TREP0002970 – SANDOZ-TREP0007852.

(b) Any other documents or things upon which Sandoz intends to rely in support of its assertion of invalidity: SANDOZ-TREP0002970 – SANDOZ-TREP0007852.

Respectfully submitted,

Dated: September 7, 2012

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CERTIFICATE OF SERVICE

I certify that on September 7, 2012, a copy of the foregoing DEFENDANT SANDOZ INC.'S INVALIDITY CONTENTIONS was served on principal counsel of record as set forth below via email.

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